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[*May 24, continued*]

The Chronic Pneumonias

By J. G. SCADDING, M.D., M.R.C.P.

"PNEUMONIA" means inflammation of the lung; but by convention, the term has been confined to those forms of inflammation which are predominantly characterized by exudation into the pulmonary alveoli. "Chronic pneumonia" thus denotes a chronic inflammation in which exudation into the pulmonary alveoli is the primary process, with organization leading to fibrosis and suppuration leading to abscess-formation as possible secondary processes, resolution being possible at any stage with more or less residual fibrosis.

While these pathological processes are well known, current textbooks of medicine do not recognize chronic pneumonia as a clinical process; it is generally dismissed as synonymous with fibrosis of the lung or chronic interstitial pneumonia—a static end-result which, it is stated, may be a very rare sequel of acute pneumonias. The only other type of chronic disease regarded as pneumonic is delayed resolution of acute lobar pneumonia.

In the nineteenth century, relatively more interest was displayed in the clinical aspects of the chronic pneumonias. Laennec (1826) described chronic pneumonia following acute pneumonia, comparable with that observed round abscess cavities; he recognized the long and often recrudescent course of these cases, but regarded them as probably consequent upon an originally acute process. Later authors entered into controversy about the clinical aspects of what was regarded as the well-established pathological entity of chronic indurative or chronic organizing pneumonia; did the condition necessarily begin with an acute phase? and if so, what were the factors that determined its lapse into a chronic phase? or could it arise insidiously as a chronic condition? This old controversy has more recently been reviewed by Milne (1911) and Floyd (1922). They approached the question chiefly from the pathological standpoint, but between them their papers give clinical histories of 19 cases in which a pathological diagnosis of organizing pneumonia was made; in

nine of these the onset of symptoms was insidious, without an acute pneumonic phase.

The main pathological feature of the cases discussed by these observers was organization of exudate, but the tendency to abscess-formation was also recognized. A rarer pathological type of chronic pneumonia characterized by the presence of foreign-body giant cells in the alveolar exudate has been described by Hecht (1910) in children; Dugge (1930) reported a case in an adult, and Cabot case No. 20092 (Case records of the Massachusetts General Hospital, 1934) is probably another example of this chronic giant-cell pneumonia. The possible chronic phase of Friedländer pneumonia, which has been described by Collins and Kornblum (1929) and by Belk (1926), must also be mentioned; this is characterized rather by a tendency to formation of chronic abscess cavities, and closely simulates chronic pulmonary tuberculosis.

My own interest in the chronic pneumonias was first aroused by three cases which I reported in 1936 under the title of "Chronic Diffuse Bronchopneumonia". During life, they had run a chronic course of two years, seven months, and three and a half months respectively, to a fatal termination, and had simulated pulmonary tuberculosis in many respects, both clinically and radiologically. At autopsy the essential lesion was a pneumonia in widespread foci, showing an unusual variety of modes of progress and spread; early consolidation, resolving consolidation, organization and suppuration being present in different foci and even in different parts of the same focus. Several similar cases were found on searching the literature.

These cases seemed important because they showed that it was possible to admit chronic pneumonia as a clinically recognizable cause of long-continued, possibly progressive or recrudescent, pulmonary inflammations. The distribution of the lesions in scattered foci is rare, but subsequent experience has suggested that a large number of more circumscribed chronic pulmonary inflammations are most logically described as chronic pneumonias, and probably have a similar morbid anatomical basis. It is the purpose of this paper to draw attention to some of these from the clinical viewpoint; it is based on the study of eight such cases admitted to Hammersmith Hospital in the past three years.

Chronic Circumscribed Non-suppurative Pneumonia

The usual type of delayed resolution of acute pneumonia falls into this group. While resolution of lobar pneumonia is usually complete within two to three weeks from defervescence, observers who have made radiological studies agree that complete clearing of the abnormal opacities may be much delayed and yet eventually be complete. Thus Graeser, Wu, and Robertson (1934), saw a lobar pneumonia in which resolution was delayed for eighty-five days, and Davies, Hodgson, and Whitby (1935), record similar delay for seventy-two days in a case of Type III pneumococcus pneumonia. The exact pathological changes in the consolidated lung in this "unresolved" state form an interesting subject for speculation. Since complete clearing without gross fibrosis is possible, it is clear that no organization and only very little suppuration is taking place, the consolidation remaining for long periods in a state of suspended activity. A similar condition of subacute or chronic consolidation, capable of complete resolution, can arise insidiously or with only mild symptoms at the onset; where such a condition persists for a long time, a very confusing clinical picture is presented, as in the following case:—

Case I.—A clerk aged 56 years was admitted to Hammersmith Hospital on June 4, 1935, with a history of increasing weakness and lassitude for eighteen months, with loss of over a stone in weight, and of more acute symptoms for seven days, starting with aching in the limbs and one attack of vomiting, and continuing with great increase in lassitude and cough,

mainly unproductive. The previous history gave no relevant information; his father had died of "consumption".

On admission he was afebrile, and remained so, but he looked pale and ill; there was dyspnœa on slight exertion and evidence of recent loss of weight. The only abnormal physical signs were in the respiratory system; there was diminished movement of the right side of the chest and marked dullness on the right side posteriorly, with weak breath-sounds, bronchial in character, in the interscapular region; no added sounds were audible. Examination of the scanty sputum for tubercle bacilli was negative; a very mixed bacterial flora was found, including coarse spirochætes and fusiform bacilli in the direct smear. Skiagrams (figs. 1 and 2) showed restriction of the movement of the right diaphragm and

FIG. 1.—Case I: June 6, 1935.

slight displacement of the mediastinum to the right; extending out from the right hilar region, an irregular shadow, mainly posterior in position. These appearances were thought to be very suggestive of a pulmonary new growth. Bronchoscopy revealed a normal bronchial tree; not only was there no evidence of bronchial carcinoma, but the mucosa appeared quite healthy and there was no excessive secretion. He was discharged from hospital on June 23, little change in the condition, either local or general, having occurred. He was next seen in the out-patient department on July 30, much improved. He felt more energetic, had no cough, and had gained 12 lb. in weight. Examination of the chest showed abnormal physical signs of the same type as previously, but diminished in intensity. A

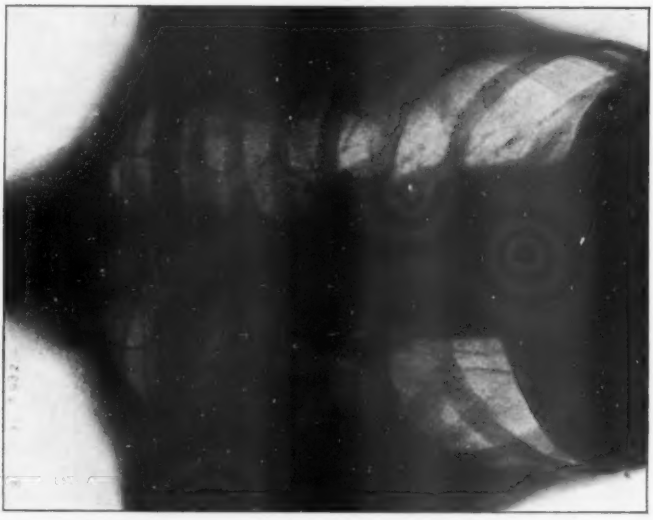

FIG. 3.—Case I: July 30, 1935.

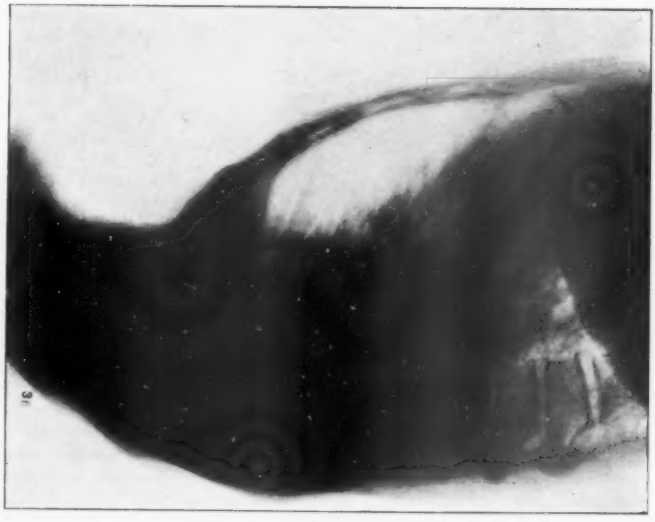

FIG. 2.—Case I: June 6, 1935. Lateral view

skiagram (fig. 3) showed considerable clearing of the abnormal shadowing in the right lung. His further course was one of progressive improvement, and a skiagram taken in November 1935 showed complete resolution (fig. 4). He was last seen over two years later, in January 1938, when the chest was still normal on both clinical and radiological examination.

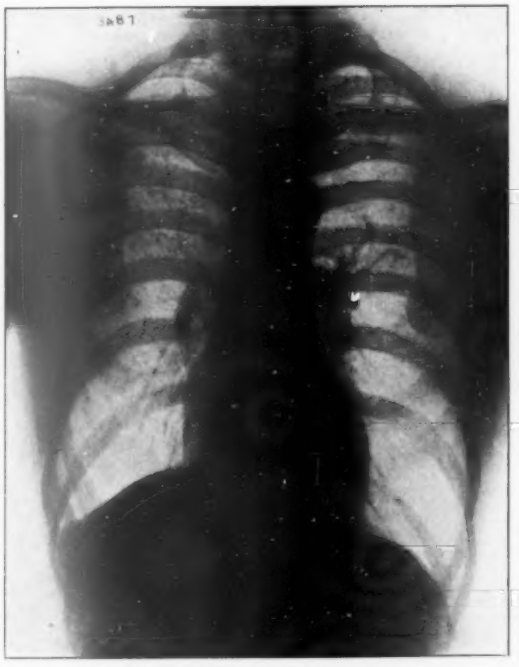

FIG. 4.—Case I: November 30, 1935.

This was clearly a case of an extensive consolidation, arising insidiously, persisting in a state of "non-resolution" for several weeks, and then slowly clearing by absorption of alveolar exudate without organization in any part. Suppuration also can have been only a very insignificant feature, if it occurred at all; in spite of the small areas in the second skiagram suggestive of minute cavities, there was never more than a very little mucopurulent sputum.

CHRONIC SUPPURATIVE PNEUMONIA

When a consolidation, at first of similar type, does not resolve completely, both organization (or fibrosis) and suppuration may occur. Clinically, the picture of suppuration is the more prominent, giving rise to obvious symptoms, and I therefore term the condition "chronic suppurative pneumonia". But gross abscess-formation may not occur, and even if it does, is fundamentally an incident in the course of a chronic organizing and suppurating pneumonia.

Chronic Suppurative Pneumonia without Gross Abscess-Formation.

Case II.—A clerk aged 58 was admitted to Hammersmith Hospital on July 1, 1937. For about a year he had not been in his usual health, suffering from abdominal pain and some loss of weight. About March 1937 he had a "chill" followed by pain in the right chest and shoulder, lasting two weeks. About the middle of June 1937 this pain returned, and after a day was followed by malaise and generalized aching pains which eventually caused him to be confined to bed. Four days before admission, a cough with scanty inoffensive sputum developed, and the pain in the chest acquired a more sharp, stabbing character. He had had no serious illnesses previously, and his family history was good.

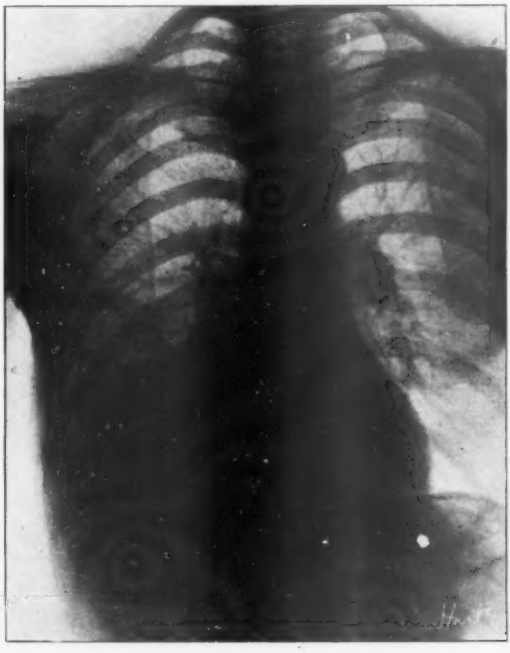

FIG. 5.—Case II: July 8, 1937.

On admission, he was pale, thin and febrile; temperature swinging irregularly up to 101° F. There was no clubbing. On examination, the chest was found to be of rigid type, with diminished movement, dullness, weak air-entry, and crepitant râles at the right base extending round to the axilla, where a pleural rub was audible. Other systems were essentially normal. The sputum was scanty and mucopurulent, contained no acid-fast bacilli, and yielded micrococci and *Strep. viridans* on culture. The leucocytes numbered 23,000 per c.mm., of which 80% were polymorphonuclear. A skiagram (fig. 5) showed consolidation in the right lower zone.

The condition remained practically unchanged until July 21, when there was pleuritic pain in the right side of the chest, and the physical signs indicated an extension upwards of the process in the right lung. A skiagram taken on July 26 (fig. 6) confirmed this, showing further consolidation. Needling in the lower axilla posteriorly failed to find fluid. The general condition remained much the same; fever was irregular up to 101° F., with occasional

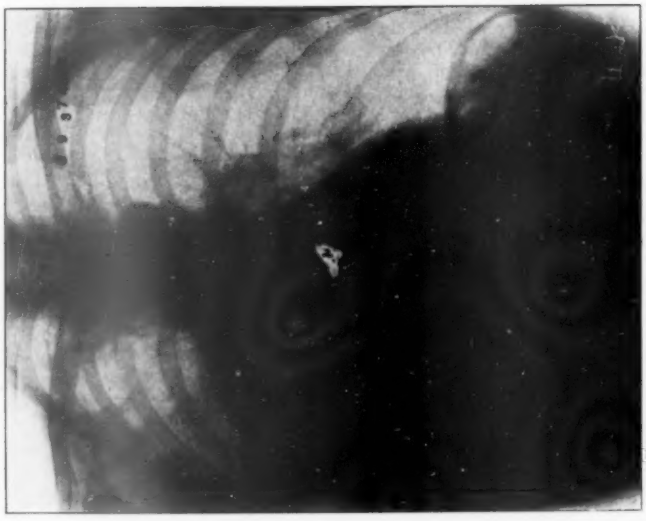

FIG. 7.—Case II: Sept. 8, 1937.

FIG. 6.—Case II: July 26, 1937.

intervals of a few days when the temperature remained below 99° F.; the sputum had become somewhat more profuse and purulent, but was never malodorous. On August 11 bronchoscopy showed inflammatory changes in all branches of the right descending bronchus, with purulent secretion in all, but no evidence of malignant disease. After this, he was treated by continuous postural drainage on a Nelson bed. Slight improvement followed, but the temperature did not settle until the beginning of September. The dullness diminished at the right base, but remained in the lower axilla, where for some time a localized area of tubular breath-sounds appeared, and numerous coarse râles were audible over the whole affected area. Moderate clubbing of the fingers was developing. On September 8, a skiagram showed considerable clearing of the consolidated areas, with some fibrosis (fig. 7). About the middle of September definite improvement began with rapid gain of weight and diminution in extent of abnormal physical signs, confirmed by a further skiagram on October 6 (fig. 8) which showed only fibrosis at the right base. He was discharged on

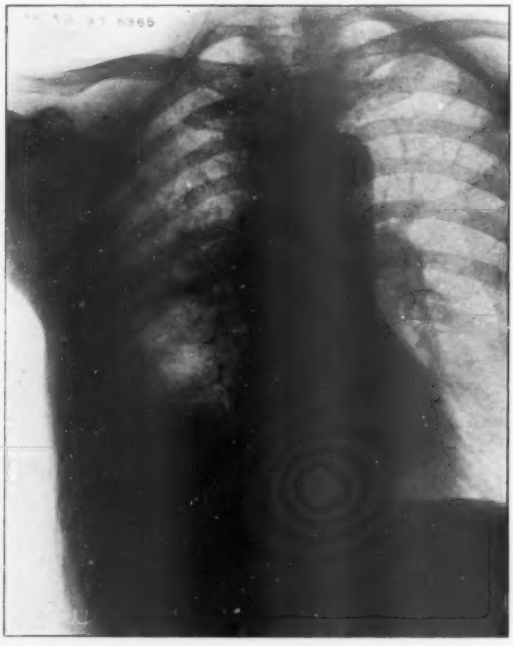

FIG. 8.—Case II: October 6, 1937.

October 30, in very good general condition, having gained over a stone in weight, and having only a trace of sputum daily. Followed-up in the out-patients' department, he has maintained this improvement, apart from a transient return of cough, sputum and pain in the right side, with some hæmoptysis in December; there was no deterioration in the general condition.

In this case, organization was the predominant feature, though small foci of suppuration probably occurred also. In a commoner type of case, of which the following is an example, detectable abscess cavities appear, often transiently, during the course of the disease.

Chronic Suppurative Pneumonia with Abscess-Formation

Case III.—A man aged 52, by occupation a polisher, had been subject to winter coughs since 1920. In April 1937, with an exacerbation of his cough, he developed a pleuritic pain in the right side of the chest, and there was increasing weakness and loss of weight. His family history was not relevant.

A skiagram (fig. 9) taken at Bethnal Green Hospital on April 26, revealed an area of opacity suggesting consolidation in the right middle zone. When admitted on May 1, he was thin and pale, and had a cough with purulent sputum. Repeated examination of the sputum was negative for tubercle bacilli, even on guinea-pig inoculation. The chart showed an irregular swinging temperature up to 99°–102° in the evenings. A skiagram on May 4 (fig. 10) showed a small cavity in the centre of the area of consolidation. After lipiodol injection on May 14, no lipiodol entered the consolidated area, but it was seen that the area of consolidation had extended. About this time there was some hæmoptysis.

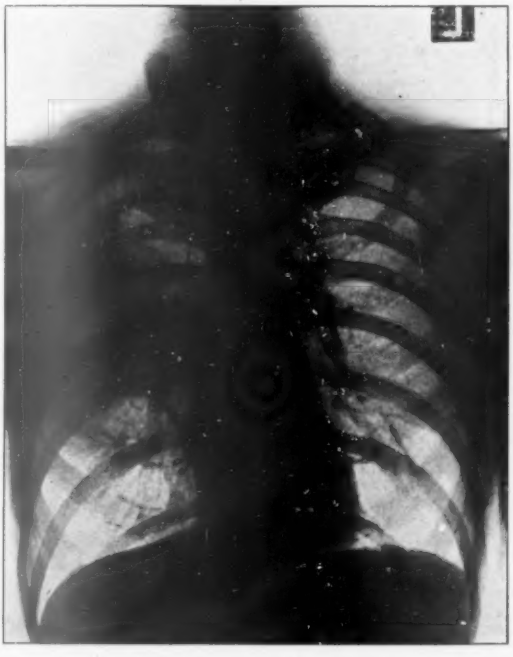

FIG. 9.—Case III : April 26, 1937.

Both physical and radiological examination showed great extension of the consolidation in the right upper lobe. The general condition, pyrexia, and local signs remained almost unchanged until, at the beginning of August, a further increase in the extent of the lesion occurred, as seen in a skiagram on August 12 (fig. 11), which also showed that some fibrosis was occurring as the trachea was being pulled over to the right. At the beginning of September, after four months of continuous pyrexia, the temperature began to settle.

On September 14 he was transferred to Hammersmith Hospital. He was then afebrile, but still thin and pale. There were signs suggestive of fibrosis at the right apex. Examination of the sputum showed no tubercle bacilli, and on culture on five occasions, a normal flora, consisting of *Strep. viridans*, Gram-negative cocci and micrococci, predominated, with.

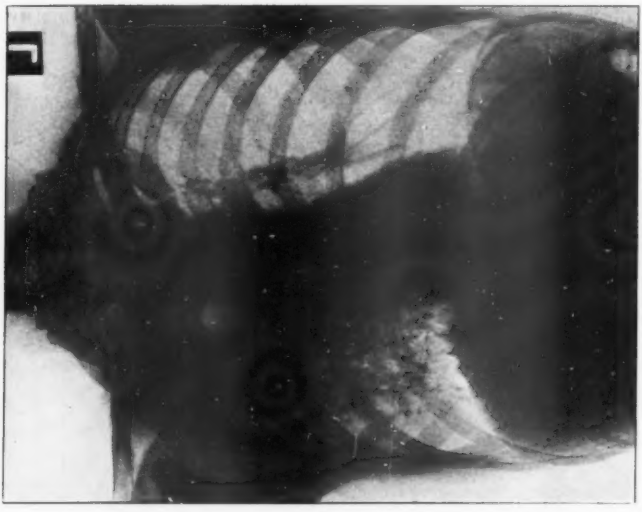

FIG. 11.—Case III: August 12, 1937.

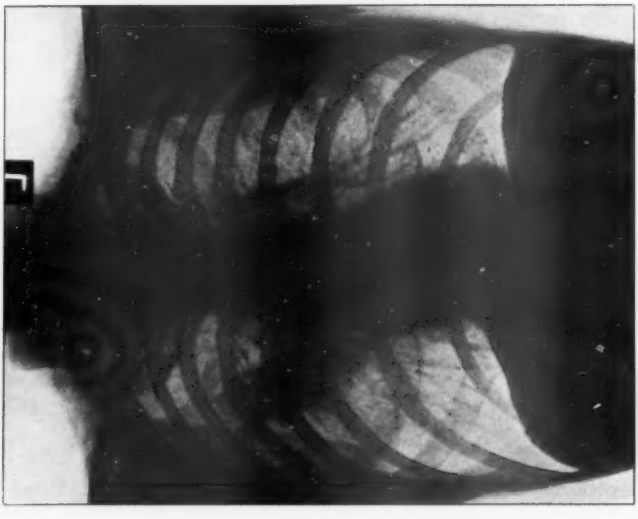

FIG. 10.—Case III: May 4, 1937.

on one occasion each, *Staph. aureus* and *H. influenzæ*. Bronchoscopy on October 4 showed no evidence of neoplasm, but inflammatory changes in the mucosa around the right upper lobe bronchus. The subsequent course was one of continued improvement, with a gain in weight of over a stone, and almost complete cessation of expectoration. A skiagram on October 20 (fig. 12) showed only some residual fibrosis at the right upper and middle zones. The patient was discharged on November 13, and when last seen as an out-patient on May 7, 1938, said that there had been no recurrence of pulmonary symptoms.

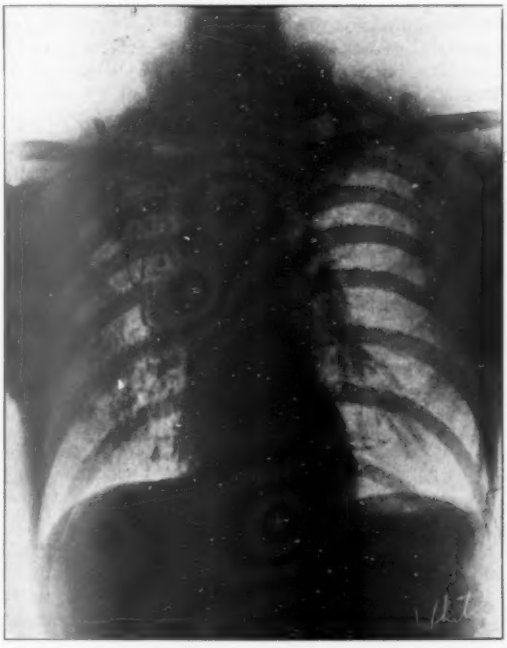

FIG. 12.—Case III: October 20, 1937.

This case illustrates well the characteristics of this not uncommon group: the irregular consolidation, with incidental breaking-down of a small area into an abscess cavity, and the tendency to spread in the form of fresh areas of consolidation which may or may not break down into abscesses. The spread is sometimes more spectacular, into another lobe of the lung; I have still under observation a patient in whom a chronic suppurative pneumonia has wandered from its original site in the dorsal part of the right lower lobe successively into the axillary part of the upper lobe, the pectoral part of the upper lobe, and finally into the middle lobe; only in the second of these situations was a small abscess cavity transiently visible.

Pulmonary Abscess of Obscure Origin

All observers who have studied large series of cases of pulmonary abscess are agreed that a large proportion of them are of obscure origin, apparently arising *de novo* without evidence of aspiration or embolism. Thus, King and Lord (1934) found that the ætiology was uncertain in 35·2% of 227 cases; Maxwell (1934) found that of 199 single abscesses 21·5% followed "acute pulmonary inflammations" and 8%

were " primary " ; Cutler and Gross (1936) found 28% of 90 cases were due to " pneumonia " and 14% of unknown ætiology ; and Allen and Blackman (1936) found that of 100 cases, 38% were of insidious onset and 18% followed an apparent pneumonia. I believe that many of these cases should be considered primarily as cases of chronic suppurative pneumonia with abscess-formation. The symptoms of the abscess dominate the clinical picture ; if the case comes to autopsy, the large abscess cavity which is by then likely to be present is apt to be named as the primary lesion, and the chronic pneumonic changes around it described as secondary. It is possible that special examination, by tomography for example, might demonstrate small cavities in some of the cases that I classify as " without gross abscess-formation"; this would not invalidate, but rather support, the thesis that the abscess-formation is only an incident in the course of chronic suppurative pneumonia. Clearly, where the process of abscess-formation is well advanced, it is reasonable to think of the case from the clinical, and especially the therapeutic, point of view, as one of lung abscess ; but the realization that the process at work is essentially one of chronic suppurative and organizing pneumonia does much to render comprehensible the frequently puzzling behaviour of the so-called " lung abscess of unknown origin ". Pathologically the importance of the chronic pneumonic process in these cases has recently been stressed by Durand (1937) ; discussing abscesses of the lung he describes a group under the title " pyosclerosis ", in which he conceives the essential process to be a pneumonia undergoing both abscess-formation and organization in varying proportions. Laennec (1826) described abscesses of the lung occurring in the course of chronic pneumonia, and his description of the morbid anatomy of the latter condition is so similar to my concept of the state of the lung in chronic suppurative pneumonia that I quote it. He says :—

" J'ai trouvé des portions d'une consistence plus ferme et moins humide que dans l'hépatisation aiguë. . . . Le tissue pulmonaire, dans leurs intervalles, était fortement infiltré d'une sérosité mêlée de petits points puriformes plutôt suspendus que dissous, et qui me parait indiquer . . . la résolution d'une péripneumonie qui était arrivée au degré de suppuration."

Ætiology of Chronic Suppurative Pneumonia

With regard to the relation of chronic suppurative pneumonia to other pneumonic processes, it may be agreed that it hardly ever directly follows an acute pneumococcal pneumonia. In the rare cases in which cavity formation occurs during the course of a pneumococcal pneumonia, it appears in the benign form which has been described by Kessel (1930) as " aputrid pulmonary necrosis ". The relation of suppurative pneumonia to the benign circumscribed pneumonias recently described under the title of " pneumonitis " (Allen (1936), Gill (1938)) is a matter for further observation.

From the bacteriological point of view, the findings are inconclusive. Analysing the results of repeated sputum examination in seven cases of chronic suppurative pneumonia, four with, and three without, gross abscess-formation I find :—

Strep. viridans in seven cases ; Gram-negative diplococci in five cases ; micrococci in four cases ; non-hæmolytic streptococci in three cases ; *Staph. aureus* in three cases ; pneumococcus in one case ; *H. influenzæ* in one case ; Vincent's spirochætes and fusiform bacilli in four cases.

There was no correlation between the clinical course of the disease and the bacteriology. Even Vincent's organisms, to which such importance has been attributed by some observers, especially by Kline and Berger (1935), seemed to play the part of important secondary invaders.

Treatment of the Chronic Pneumonias

Non-suppurative types.—There are no very clear indications for treatment for these except general and symptomatic treatment.

Suppurative types.—In these, continuous postural drainage, according to the principles expounded by Nelson (1934), is often of value even in the absence of gross abscess-formation. At bronchoscopy in these cases purulent secretion is usually to be seen coming from one or more bronchi, and it seems reasonable to secure continuous drainage of this by suitable posture. If a localized abscess forms and is not draining through the bronchial tree, it must be drained surgically on the usual principles, but the results of surgical drainage in the diffuse suppurative pneumonias, even with definite abscess-formation, are, in my experience, less satisfactory than those obtained in the case of more definite abscesses of clear ætiology. In the present series of eight cases, of which five fell into the group of suppurative pneumonia with abscess-formation, two of the latter were treated surgically; in one, drainage was not completed, on account of the onset of a pleural effusion, but temporary improvement occurred; in both, further spread of suppurative consolidation to other lobes eventually occurred, with fatal termination. When it is realized that the suppuration is only a part of the process, the often limited improvement obtained by drainage, either externally or through the bronchi, is understandable.

Treatment by the arsenical preparations has not in my hands effected more than temporary improvement, even in cases showing large numbers of Vincent's organisms in the sputum; the dramatic results recorded by Kline and Berger have not been paralleled, even with dosage as heavy as 0·6 grm. of novarsenobillon intravenously every other day, for five doses.

Sulphanilamide, also, proved disappointing in two typical cases of chronic suppurative pneumonia, in which no improvement at all was noted following its administration in doses of 1·0 grm. thrice daily by mouth.

Among supportive measures, blood transfusion is an important aid, and should be employed when the hæmoglobin level falls and cannot be restored by other means.

In conclusion: As the result of the study of eight cases I have tried to present from the clinical aspect a series of types of chronic pneumonia, each apparently capable of arising as a primary process; ranging from a non-suppurative type having affinities with delayed resolution of acute pneumonia, to a suppurative type with abscess-formation which would usually be described as one of the types of pulmonary abscess. It is suggested that in the latter type the re-orientation of outlook is helpful in understanding the course of the disease.

[I am indebted to Dr. W. P. Greenwood, Medical Superintendent of Bethnal Green Hospital, for permission to refer to the course of Case III while under treatment at that hospital; and to the Chief Medical Officer, L.C.C., for permission to publish the case-reports.]

REFERENCES

Allen, C. I., and Blackman, J. F. (1936), *J. Thoracic Surg.*, **6**, 156.
Allen, W. H. (1936), *Ann. Int. Med.*, **10**, 441.
Belk, W. P. (1926), *J. Infect. Dis.*, **38**, 115.
Cabot case No. 20092 (1934), *New England J. Med.*, **210**, 487.
Collins, L. H., and Kornblum, K. (1929), *Arch. Int. Med.*, **53**, 249.
Cutler, E. C. and Gross, R. E. (1936), *J. Thoracic Surg.*, **6**. 125.
Davies, D. T., Hodgson, H. G., and Whitby, L. E. H. (1935), *Lancet* (i), 919.
Dugge, M. (1930), *Virchows Arch. f. path. Anat.*, **277**, 757.
Durand, H. (1937), *Arch. méd.-chir. de l'app. respir.*, **12**, 81.
Floyd, R. (1922), *Am. J. M. Sc.*, **163**, 527.
Gill, A. M. (1938), *Brit. M. J.* (i), 504.
Graeser, J. B., Wu, C., and Robertson, O. H. (1934), *Arch. Int. Med.*, **53**, 249.
Hecht, V. (1910), *Beitr. z. path. Anat. u. z. allg. Path.*, **48**, 263.
Kessel, L. (1930), *Arch. Int. Med.*, **45**, 401.
King, D. S., and Lord, F. T. (1934), *Ann. Int. Med.*, **8**, 468.
Kline, B. S., and Berger, S. S. (1935), *Arch. Int. Med.*, **56**, 753.
Laennec, R. T. H. (1826), "Traité de l'auscultation médiate". Paris, 2nd. ed. vol. I, p. 475.
Maxwell, J. (1934), *Quart. J. Med.* (N.S.), **3**, 467.
Milne, L. S. (1911), *Am. J. M. Sc.*, **142**, 408.
Nelson, H. P. (1934), *Brit. M. J.* (ii), 251.
Scadding, J. G. (1936), *Brit. J. Tuberc.*, **30**, 186.
Id. (1937), *Brit. M. J.* (ii), 956.

Some Aspects of Post-operative Pulmonary Complications

By N. C. Oswald, M.B.

Summary

Observations were made upon the chests of all patients who underwent abdominal operations during one complete year at Charing Cross Hospital. Altogether 710 cases were studied, and in 75 (11%) of these, pulmonary complications developed. For appendicectomy and herniorrhaphy the incidence was about 5%, and rose to 20% or 30% for operations upon the upper abdomen. The highest incidence was found after perforated peptic ulcer.

Age.—In dividing the present series into those below and those over 40, it was found that the incidence of pulmonary complications was twice as great in the older group. This, however, does not represent the true state of affairs, as a relatively greater number of extensive operations are performed after the age of 40, and if we divide all operations arbitrarily under two headings, "large" and "small", according to their extent, we find that under the former heading there is no difference in the incidence in the two age-groups, whereas for the smaller operations, patients over 40 show rather more than twice as many complications as those under 40. These findings were rather surprising and are a little difficult to explain, but, provided the figures are sufficiently large to be reasonably reliable, they may be accounted for to some extent by the fact that, regardless of the age of the patient, an extensive operation produces a considerable amount of shock and muscular inertia for some twenty-four to forty-eight hours; and this is precisely the time during which the complications develop.

Deaths.—In the present series some 36 patients (5%) failed to survive abdominal section; in four of these the chest was the sole cause of death; in a further nine it was a contributing cause of death; four patients died from pulmonary embolism. The remaining 19 died from conditions unrelated to the lungs. Of the four cases in which the chest was considered to be the sole cause of death, the youngest patient was 48 and the oldest 66.

The inference, of course, is that in the event of an extensive surgical procedure being undertaken, though older people do not seem to be particularly prone to pulmonary complications, they do not show the same ability to overcome them once they have developed.

That four patients out of 36 should die of pulmonary embolism, seems at first sight to be rather a generous proportion, particularly as this series takes no account of gynæcological operations. For confirmation of this proportion it was decided to consult post-mortem records. Notes on some 263 patients who had failed to survive abdominal surgery during the last four years were studied; of these, 24 died of pulmonary embolism, giving a percentage of 10.

Hence, one is led to suspect that the number of cases in which the chest can be considered the sole cause of death is roughly equal to the number in which the patients die from a pulmonary embolism, and therefore, more attention should be directed towards such prophylactic treatment as is available for the latter condition, in the form of massage and exercises to the lower limbs and later the abdomen.

A further conclusion which may be drawn from this analysis of post-mortem records is that about 20% of all patients who die as a result of abdominal surgery will show a considerable amount of disease in the pulmonary parenchyma.

No difference in incidence was noted after spinal injections as compared with general anæsthesia.

There was no marked seasonal variation.

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PLATE I.

FIG. 1.—Foot of a normal child.

FIG. 2.—Foot of a child with the same condition as that of Mrs. M., taken as nearly as possible in the same angle as fig. 1. Note the relationship of the first metatarsal head to the others.

FIG. 3.—Lateral view of patient's left foot before operation. Note the plane of the 1st metatarsal bone, and that the 2nd metatarsal head is clearly visible.

FIG. 4.—After operation. Note: (1) The graft consolidated. (2) The altered alignment of the 1st metatarsal bone. (3) The 2nd metatarsal bone is no longer visible, i.e. the head of the 1st metatarsal bone has been depressed.

PLATE II.

FIG. 5.—Right foot after operation.

FIG. 6.—Right foot not yet operated on. Note the hallux flexus attitude; the 1st metatarsal bone is not bearing weight.

(*a*)

(*b*)

FIG. 7 (*a*) and (*b*). Same foot after operation.

Section of Orthopædics

President—A. Rocyn Jones, F.R.C.S.

[*January* 4, 1938]

Metatarsus Primus Elevatus.—C. Lambrinudi, F.R.C.S.

The patient, Mrs. M., consulted me on account of the extreme fatigue in her feet which she experienced after walking about a quarter of a mile. She had no particular local pain but the fatigue was sufficient to interfere with her normal life and happiness. One suggestive remark she made was that her feet wobbled and felt unstable. Her unsteadiness was very evident when she walked; she appeared to have a hallux flexus but no rigidity, and on closer inspection it seemed as if the head of the 1st metatarsal bone was lying on a higher plane than that of the other four—so much so that when she wobbled she flexed her big toe at the metatarsophalangeal joint in order to balance herself. It was her inability to balance that seemed to be the main trouble. The 1st metatarsal head being on a higher plane, she could bring the inner segment of the foot into action only by flexing the big toe at the metatarsophalangeal joint.

Through a dorsal incision I exposed the metatarsophalangeal joint and by depressing that bone so as to make the head of the 1st metatarsal come into alignment with the others, a gap of quite $\frac{1}{3}$ in. was left. This was filled up with bone graft and the foot put in plaster—a perfectly simple operation. I dealt with the left foot first. The deformity was quite corrected and the foot was so comfortable that she asked me to treat the right one in the same way (*see* Plates I and II).

I believe this is an instructive case, as it is quite possible that such a condition may be responsible for a certain number of cases of hallux rigidus occurring in later life. It may also explain the common association of hallux rigidus and valgus foot, since it is only by putting the foot in valgus that the 1st metatarsal head can bear weight. Morton has suggested hypermobility of the inner segment of the foot as a cause of weakness and pain, but at the operation the joint seemed perfectly stable.

The skiagram of the foot of a child of 14 (*see* Plate I) shows a condition almost identical with that of Mrs. M.—a fact which suggests that the deformity is congenital.

Reports on the following cases were also given, with demonstrations:—

(1) Fragilitas Ossium. (2) Dystrophy of Bone.—G. F. G. Batchelor, F.R.C.S.

(1) Fracture of Ankle with Spina Bifida. (2) Myositis Ossificans of Adductors. (3) Traumatic Periostitis of Tibia.—E. P. Brockman, M.Ch.

Pathological Fracture of Humerus (further report on case shown November 2, 1937).—F. F. Rundle, F.R.C.S.

Pellegrini-Stieda Disease.—Erna H. Jebens, F.R.C.S.

(1) Fracture Dislocation of Ankle. (2) Giant Cell Tumour, Upper End of Tibia: Skiagrams to show progress. (3) Giant Cell Tumour at Lower End of Femur. (4) Subperiosteal Incarceration of Fractured Capitellum.—Norman Capener, F.R.C.S.

Fracture Dislocation of Spine.—B. Whitchurch Howell, F.R.C.S.

[*May* 3, 1938]

Crush Fracture of the 12th Dorsal Vertebra with Complete Paraplegia.—A. Rocyn Jones, F.R.C.S.

The patient, a man aged 33, was admitted to the L.C.C. Fulham Hospital on December 12, 1937, immediately following an injury to his spine sustained while he was repairing a defect of an elevator. For this work he stood with one foot on a landing floor and the other on the floor of the elevator, about 12 in. below. Suddenly the elevator descended and he was caught between its roof and the landing floor. He managed to struggle into the elevator, within which he was found, collapsed, when it reached the ground floor of the building.

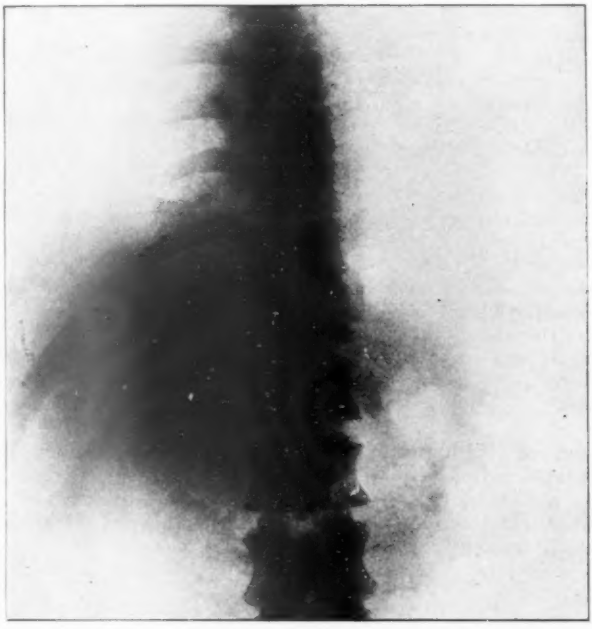
On admission to hospital he was suffering from severe shock and there was a flaccid paralysis of both lower limbs. The ankle, knee, and plantar reflexes were absent, and there was pin-prick anæsthesia of the outer surface of the thighs, legs, and scrotum. Two hours later, deep sensibility and joint sense were present in the lower limbs; the level of anæsthesia extended to 5 in. above the knee on the left side and to the level of the knee on the right side. The flaccid paralysis was unchanged and the deep reflexes remained absent. Fifteen hours after admission slight voluntary movements in the toes were visible; anæsthesia on the right side was limited to the foot only, but was unchanged on the left side. There was retention of urine and catheterization was started. The next day paralysis was again complete, sensory loss extended up to D.12 and L.1, and incomplete loss one segment higher; knee, ankle, and plantar reflexes were still absent. Catheterization was performed at eight-hourly intervals; there was incontinence of fæces. A skiagram revealed a crush fracture of D.V.12; there was no displacement, neither was there much diminution in the size or much alteration in the shape of the vetebra. In fact, the radiographic signs alone would not have led one to expect such grave nervous symptoms as were present; the paraplegia appeared to bear no proper relation to the degree of vertebral destruction.

The patient was too ill for any attempt to be made at correction by means of a plaster-of-Paris jacket applied in hyperextension, even if such treatment had offered any hope of relief from the paralysis. His condition remained unchanged for a week, and then a sore developed over the sacrum. Thereupon he was nursed on an anterior plaster-of-Paris shell during the day and turned over on his back at night. Complete paraplegia persisted from the level of D.12 downwards. In three weeks urinary infection set in, but five weeks after the injury he was able to pass urine without the aid of a catheter, owing to the development of an automatic bladder. Four days from the beginning of independent micturition the fundus of the bladder ruptured, giving rise to generalized peritonitis. He died twenty-four hours later.

Autopsy.—A crush fracture of D.V.12, with no displacement, was revealed. The spinal canal was not encroached upon by the fractured vertebra. There was some bruising of the anterior and posterior longitudinal ligaments but no breach of continuity. The dura mater at the site of fracture showed no sign of injury but the spinal cord within showed complete degeneration at that level. The bladder showed very marked cystitis with necrotic areas at the fundus. Rupture occurred at one of these necrotic areas, producing general peritonitis.

A probable explanation of the mechanism of injury is suggested by a consideration of the attitude of the man at the time of the accident. The sudden descent of the elevator flexed his head and dorsal spine acutely forward, producing a crush fracture of D.V.12 and at the same time the cord was severely compressed, causing irreparable damage to the neural elements, with complete and absolute paralysis from the

moment of injury. When he struggled free into the lift there followed a recoil of the bony framework, a restoration of the spinal canal, and possibly even some expansion of the crushed vertebra. But the crushed cord could not recover. This



Radiograph indicating a crush fracture of the 12th dorsal vertebra. There is not much diminution in size or shape of the bone, but there was an irreparable injury to the spinal cord, with a profound paraplegia.

probably is the reason for the apparent discrepancy between the severity of the palsy and the mildly crushed appearance of the vertebra in the radiograph (*see* figure).

Pathological Fracture of the Right Humerus.—K. H. Pridie, F.R.C.S.

Philip P., aged 32, admitted to Bristol Royal Infirmary, 21.1.38.

History.—Twenty-three years ago, patient sustained an injury to the right leg, which discharged for about six weeks. Nothing is known about the treatment, but as the right leg is fixed by bony ankylosis, there appears to have been a dislocation of the hip which is fixed in adduction.

Ten years ago patient appears to have again injured the right leg, and was in the Bristol Royal Infirmary for one week, during which time an abscess burst spontaneously. (The skiagram taken on 21.1.38 (fig. 1, Plate III) would suggest that he had septic arthritis of the right hip.) The patient has been well since, but he is a pale, thin, ill-looking man. He has, however, been able to do hard work, involving very heavy lifting.

Present condition.—Four weeks previous to his admission to the Infirmary in January 1938 he had had pain "like rheumatism" in the right arm. Two weeks later the arm was examined by X-rays and the skiagram was passed by the casualty officer as "normal," but on looking carefully into it (fig. 2, Plate III) one can see a thickening of the cortex of the humerus, and in the centre of the shaft there is a suspicion of a Brodie's abscess.

Fourteen days later the patient was admitted into hospital, with a temperature of 99° and a spontaneous fracture of the middle of the right humerus. The skiagrams then appeared as in fig. 3, (Plate III).

Pathological report.—"The bone tissue shows subacute osteitis, and there is similar subacute inflammatory reaction in the surrounding tissues. Gram-positive cocci are present. There is no evidence of new growth. Pathological diagnosis: Subacute staphylococcal abscess of bone."

The photomicrographs (figs. 4 and 5, Plate IV) show normal bone spicules, but the spaces between the spicules, instead of being composed of fat and marrow, show an increase of cellular tissue, similar to the reaction (fibroblastic) seen in von Recklinghausen's disease of bone, or generalized osteitis. In each picture, abscess tissue with pus-cells and staphylococci can be seen at the site marked "A".

Comment.—This case is of interest in that it shows how septic arthritis of the hip, the result of an accident twenty-three years previously, may suddenly produce metastatic abscess, followed, in a period no longer than fourteen days, by a pathological fracture.

A Method of Reduction and Fixation of Os Calcis Fractures.—F. P. Fitzgerald, F.R.C.S.(Irel.).

During the six years, 1926–1932, Böhler treated 182 fractures of the os calcis. Only five of these (3%) were of what he styles the sixth type. This type is the most difficult os calcis fracture to treat, and is said to occur only between 20 and 30 years of age (Böhler). The two cases here reported are, however, of the sixth type.

Case I.—A man, aged 48, sustained a fifth type os calcis fracture on the right, and a sixth type on the left (figs. 1A and 1B). The right was fairly easily reduced by screw traction.

On the left side, preliminary attempts to disimpact the fracture, followed by screw traction, failed. The traction was increased, and Kindersley's method of hammering the plantar surface of the heel, and application of the redresseur, was attempted and proved unavailing (figs. 2*a* and 2*b*). With the limb still in the screw traction apparatus, a short Steinmann's nail was driven into the posterior fragment of the os calcis, through the back of the heel. A nail-holder was attached and the nail plantar-flexed, thus levering the fragment into position (figs. 3*a* and 3*b*). The limb was put up in plaster incorporating all three pins to fix the position obtained.

Case II.—A man, aged 39, sustained a fracture of the left os calcis (figs. 4A and 4B).

No preliminary manipulation was attempted in this case. The three pins were inserted, and the limb placed in the screw traction apparatus to form a fulcrum for the lever. The posterior fragment was again levered into position (figs. 5A and 5B). The redresseur was applied and the limb plastered as before. Fig. 6 shows the fracture one week after reduction, the pins being retained for fixation.

Reduction was not so easily obtained as in the first case. This was probably owing to the fact that an attempt to disimpact the fragments had not been made previously.

[My thanks are due to Mr. Eric Lloyd and Mr. Henry Stokes for their kindness in allowing me to treat and report these two cases.]

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PLATE III.

21;1.38 FIG. 1.

7.1.38. FIG. 2.

21.1.38. FIG. 3.

K. H. PRIDIE: Pathological Fracture of the Right Humerus.

PLATE IV.

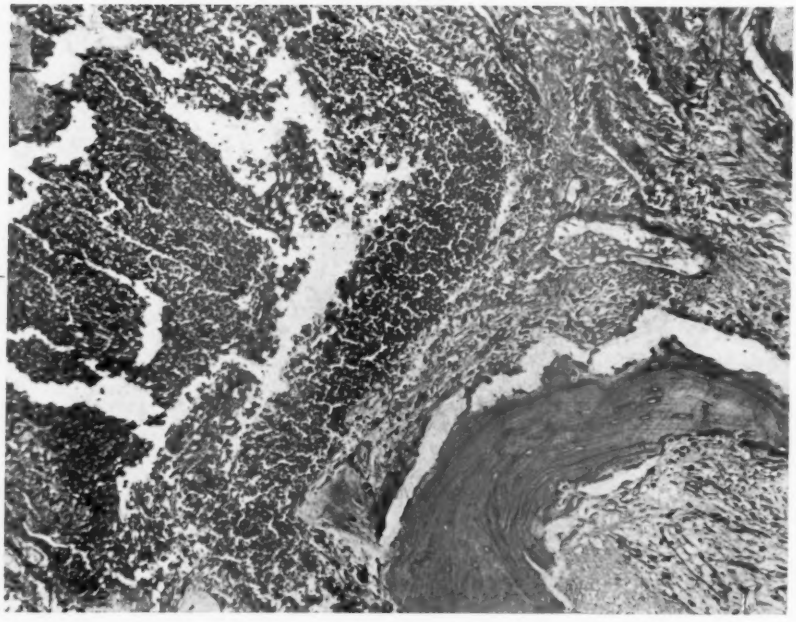

FIG. 4

FIG. 5.

K. H. PRIDIE: Pathological Fracture of the Right Humerus.

FIG. 1A.

FIG. 1B.

FIG. 1A.—Angulation of the joint surfaces between astragalus and os calcis. The anterior extremity of the posterior fragment is impacted into the fragment in front.
FIG. 1B.—Axial view, showing angulation of os calcis to line of the foot.

FIG. 2A.

FIG. 2B.

FIGS. 2A and 2B.—Angulation still present after powerful traction in both planes, and hammering the under surface of the bone. The tibia was cracked by putting the nail too far back.

F. P. FITZGERALD: A Method of Reduction and Fixation of Os Calcis Fractures.

FIG. 3A.

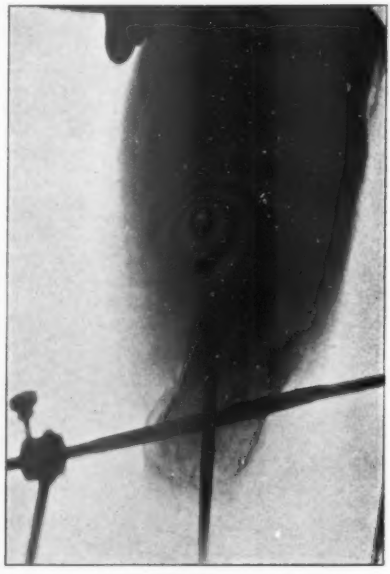

FIG. 3B.

FIG. 3A.—Showing the third nail driven into the posterior fragment, which has been levered downwards so that the joint surfaces are parallel.

FIG. 3B.—The angulation has been reduced.

FIG. 4A (Case II).—Angulation and impaction as in fig. 1.

FIG. 4B.—No angulation in this case; longitudinal fracture present.

FIG. 5A.—The tuber-joint angle is normal.

FIG. 5B.—The third nail inserted so as to avoid the longitudinal fracture.

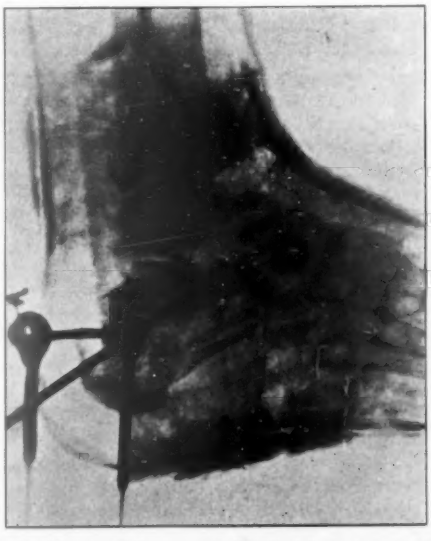

FIG. 6.—Showing the three nails incorporated in the plaster one week after reduction.

F. P. FITZGERALD: A Method of Reduction and Fixation of Os Calcis Fractures.

The following cases and skiagrams were also shown :—

Stiffness of Temporo-mandibular Joints.—A. Rocyn Jones, F.R.C.S.

Arthroplasty of the Finger.—B. Whitchurch Howell, F.R.C.S.

Skiagrams of Three Cases of Cavities in the Body of the Astragalus.—E. P. Brockman, M.Ch.

Cysts in the Carpal Scaphoid and Radial Styloid.—G. O. Tippett, F.R.C.S.

(1) Three Cases of Fracture of the Upper End of Tibia. (2) Smith-Petersen Pin for Subtrochanteric Fracture of the Femur.—John Bastow, F.R.C.S. (for C. E. Kindersley, F.R.C.S.).

(1) Brachial Vascular Disturbance following Injury. (2) Smith-Petersen Nail: A Surgical Accident. (3) Fracture Dislocation of Ankle (previously shown).—Norman Capener, F.R.C.S.

Disappearing Metacarpal.—K. H. Pridie, F.R.C.S.

Fracture of Medial Epicondyle of Humerus.—F. P. Fitzgerald, F.R.C.S.

Osteomyelitis of Os Calcis.—J. A. Cholmeley, F.R.C.S.

(1) Congenital Pes Cavus. (2) Sclerosing Changes in Pelvis.—L. H. F. Walton, M.R.C.S., L.R.C.P.

Section of Surgery

SUB-SECTION OF PROCTOLOGY

President—J. P. Lockhart-Mummery, F.R.C.S.

[*May* 11, 1938]

DISCUSSION ON URINARY FISTULÆ IN RELATION TO THE COLON AND RECTUM

Mr. H. Wade: A channel of communication between the urinary bladder and bowel may be produced in a variety of ways. It may be the result of a congenital malformation, an error of development during intra-uterine life, or it may result from trauma, by accident or operation, or the delayed action of radium. On the other hand, it may be accounted for by an inflammatory process, such as a diverticulitis of the pelvic colon, producing an abscess which has ruptured into the urinary bladder, or an abscess following acute appendicitis may cause such a fistula. Not infrequently the channel results from the breaking-down of a new growth, which most commonly arises in the colon and subsequently invades the bladder, or may under certain circumstances arise in the bladder and subsequently involve the colon.

In dealing with these cases, it is important to remember that in early intra-uterine life there is a stage when the alimentary canal and the urinary channel form a single cavity which is at first subdivided into two chambers, which ultimately come to open on to the skin surface by the formation of the urethra and the rectum and anal canal. This process may be arrested at any stage and various vesico-colonic fistulæ be thus formed. I have seen one in which a channel existed between the rectum and bladder, and another in which the communication existed between the rectum and the prostatic urethra.

In the days when the Hippocratic oath was strictly adhered to and the lithotomists travelled Europe cutting for stone, the constant approach to the urinary bladder was by the perineal route, and more recently this path of approach was very commonly employed in perineal lithotomy for the extraction of stone, when perineal cystotomy was carried out for the purpose of draining the urinary bladder, or when perineal prostatectomy was performed for removal of an innocent or malignant obstruction at the neck of the bladder.

I have never seen a fistula follow the operation of perineal lithotomy or cystotomy.

I have, however, seen such a fistula follow the operation of perineal prostatectomy : in fact it is safe to say that this most satisfactory operation, which Young did so much to popularize, has fallen into disuse, not from its lack of inherent merits, but because of the delicate technique and accurate anatomical knowledge required for its performance.

The treatment of these cases will depend, of course, upon the severity of the disability. I have known of a patient who carried on a natural life for fifteen years with a fistula between the prostatic bed and the rectum, and ultimately only sought relief owing to the formation of a urinary calculus within this channel.

The gynæcologist gets excellent results from the treatment of carcinoma of the cervix uteri by the application of radium. The emanations from this mysterious element, although doing immense good at the time, may, by their delayed action, lead to necrosis of the bladder wall, and this delayed action may only appear from two to four years after the original treatment. It is made manifest by an appearance on the bladder floor which simulates very closely that due to the development of a recurrent malignant growth. Fortunately, in the majority of cases, if left alone, in three or four months' time the necrotic area sloughs away and the mucous membrane heals over. I have, however, seen a case in which a vesico-vaginal fistula has resulted, and another in which the vaginal cavity was almost completely obliterated owing to inflammation following the application of radium, and a cavity at its upper part communicated with both the bladder and the rectum.

In the light of our present knowledge, probably the most satisfactory way of treating malignant disease of the prostate gland is by the use of radium introduced interstitially. It is a form of treatment that is safe in practice ; it undoubtedly prolongs life materially and possibly will cure certain cases, but it is important to remember some of the terrible disasters that originally followed the use of this element, and I personally think of one case in which the application of radium applied *per rectum* led to the formation of a vesico-intestinal fistula which caused severe pain and great distress to the unfortunate sufferer.

The cases of vesico-intestinal fistula that owe their origin to an inflammatory cause are, in my experience, the most common and certainly much the more satisfactory to deal with, and of these I would put first those due to diverticulitis of the pelvic colon. They are most satisfactory to deal with in that the distress they give rise to is so profound, the relief obtained so satisfactory, the treatment adopted so safe and so simple.

All the cases of this nature that I have met with occurred in males in the fifth or sixth decade of life, and on inquiry the history has usually been that of chronic constipation requiring the persistent use of aperient medicine. This period of diverticulosis was followed by a definite attack of diverticulitis—a story that suggests almost acute obstruction—which settled down and was followed by a suspicion of possible appendicitis. This stage ultimately passed off and we found the patient next suspecting that air was being voided in the urine, which was altered in appearance. The presence of air is confirmed if the patient arranges to void urine with the point of the penis immersed in a vessel of water, the escape of gas being thus demonstrated.

In my experience cystoscopic examination has revealed in most cases a remarkable absence of acute infection within the bladder wall. The power of resistance of this membrane to infection is again confirmed, and I have also found that although a suspicious area can easily be seen where the presence of the fistula is suspected, its exact situation is not easy to demarcate. I have also noted that any method wherein fluid is injected into the bowel in an effort to demonstrate this channel, whether by

inspection through a cystoscope or by X-ray examination, has been unsatisfactory. On the other hand, it is usually a simple matter to demonstrate the presence of the fistula by injecting boric lotion tinted with methylene blue into the bladder and examining with a proctoscope in the rectum, when a blue fluid is seen to flow out and the actual opening may be visualized. Although the demonstration of the channel by X-ray examination is unsatisfactory, a barium enema followed by an X-ray photograph usually confirms the diagnosis of the underlying cause, wherein the diverticulosis is revealed, an appearance which, when felt, may be compared to two strings of pearls hanging over the pelvic brim into the basin of the pelvis. Having established the diagnosis, the question of treatment of these cases arises, and I consider that by far and away the best results follow the simple proceedings of performing a colostomy and resting the inflamed part. On opening the abdomen a mass may be felt which closely simulates a new growth. It is hard in consistence. In such a case it may be confidently assumed that the condition is inflammatory, and the treatment consists of a colostomy which is most conveniently carried out in the distal transverse colon, which is far enough above the site of the diverticulitis in the pelvic colon and, at the same time, in a portion of the bowel where the intestinal content has by this time become semi-solid in consistence. The price the patient thus pays is the discomfort of a colostomy, but the reward he receives is a rapid improvement in health. Closure of the fistula occurs naturally and should it be considered advisable later on, the colostomy may be closed, but in no circumstances would I advise that this be done under a period of two or three years.

The case in which a vesico-colic fistula follows an appendicular abscess is more difficult to treat, in that it is more difficult to demonstrate the exact site of the opening into the colon, and of course if it be into the cæcum no benefit will follow from the performance of a colostomy. In such a case radical operative surgery will be necessary to excise the channel and close the two openings. If, however, in these cases it is the pelvic colon that is opened into, colostomy again is indicated and the results again prove equally satisfactory.

Vesico-intestinal Fistula associated with Malignant Disease

When during a cystoscopic examination a malignant tumour is observed growing from the roof of the urinary bladder, it is always advisable to consider the possibility of this being due to the invasion of the bladder wall from a new growth arising primarily within the abdominal cavity. This growth originates most commonly in the pelvic colon, but rarer sources of origin are met with in the intestine or, in female patients, in the ovary. It is a routine practice therefore, in these cases, to make an examination by barium enema in order to clear up this point.

Sometimes a vesico-colic fistula may result. It is produced by a perineoplastic abscess developing in the adhesions which fix the tumour of the colon to the bladder wall; the abscess ulcerates into the bladder cavity and establishes a communication with the bowel. The indications of the presence of this are similar to those noted in the former cases, except that the patient is seriously ill and there is that indefinable something which tells us that malignant disease is here confronting us. In such a case colostomy is not indicated as the operation of election. The ideal course is a laparotomy, an aseptic excision of the pelvic colon, and subsequently a partial cystectomy—removing, with the portion of bladder, the colon and its tumour. This partial cystectomy may necessitate an extensive removal of the wall of the bladder, and the size of the cavity may be very much reduced in consequence. Nature, however, very rapidly restores the cavity to its normal capacity, and ultimately it is difficult to realize the extensive operative procedure that has been carried out.

Mr. Lionel E. C. Norbury : Urinary fistulæ in connexion with the rectum and colon may be : (1) Congenital. (2) Acquired.

Congenital.—Failure of development of the longitudinal septum, which grows down in the second month of intra-uterine life and normally separates the genito-urinary canals from the rectum and anus, will permit of the bowel opening into the bladder, urethra or vagina. This deformity is often associated with imperforate anus. In such cases a colostomy will usually be necessary. In some cases at a later date the communication may be closed by operation.

Acquired.—From the proctological point of view there are two main causative factors : (*a*) Diverticulitis. (*b*) Carcinoma.

Other causes include trauma (direct or indirect), e.g. the result of a foreign body in the rectum or bladder; sitting on a spike; bullet-wound, &c.; or following perineal excision of the rectum in which the bladder or urethra may be accidentally damaged, a fistula subsequently forming between this viscus and the pelvic colon.

I have at the present time at St. Mark's Hospital a case in which I performed a perineal excision of the rectum on account of carcinoma. At the operation the growth was found to have involved the prostate. I had to remove a portion of the prostate with the rectum ; the prostatic urethra was encroached upon and could be seen lying in rather a menacing manner in the depths of the wound. Some days later a perineal urinary fistula developed, and now practically all the urine is passed through this.

Recto-urethral or recto-vesical fistulæ may follow operations upon the prostate or urethra, e.g. perineal prostatectomy, external urethrotomy ; the passage of metal catheters or bougies in certain cases of urethral stricture. In the case of recto-urethral fistula, urine only escapes *per rectum* during micturition ; in that of recto-vesical fistula urine escapes continuously into the rectum.

Again, a pelvic or prostatic abscess may rupture into the bladder and rectum, or a growth may spread from the bladder to the rectum or colon.

I propose to confine my remarks chiefly to fistulæ which are the result of diverticulitis and carcinoma of the bowel. It may be exceedingly difficult to distinguish between diverticulitis and carcinoma, even at operation, when a mass is found involving the bowel and bladder. The two conditions may co-exist. It is generally accepted, however, that the usual cause of vesico-colic fistula is diverticulitis. When it occurs in cases of malignant disease it is a late or terminal manifestation. Bladder symptoms are not at all infrequent in cases of diverticulitis of the pelvic colon—the result of inflammatory adhesions between these two structures.

One or more diverticula may form fistulous communications with the bladder, the result of ulceration or gangrene. Or again, a diverticulum may perforate with the formation of a localized abscess between the colon and bladder wall, the abscess finally discharging into the bladder. Diverticulitis most frequently involves the pelvic portion of the colon, and even in those cases in which it is more widespread throughout the large intestine, it is most advanced in the sigmoid loop. Diverticulitis very rarely involves the rectum, and so a vesico-rectal fistula from this source is a pathological curiosity.

I had, at the Royal Free Hospital, one case of perforated diverticulum of the rectum which produced a pelvic abscess and intestinal obstruction, but had not involved the bladder. I believe that a similar case occurred recently at St. Mark's Hospital.

Sex.—Diverticulitis is much more common in men, and therefore one would

expect vesico-colic fistula from this source to show a preponderance in the male sex. Statistics tend to prove this.

Age.—This varies from 30 to 60 years.

In the development of such a fistula, the sequence of events appears to be: (1) Frequency of micturition with scalding, (2) passage of pus and sometimes blood in the urine, (3) pneumaturia and definite fæcal matter. In the latter case the urine is foul-smelling and shows the presence of *B. coli*. In some cases, pneumaturia and the feeling of passing wind *per urethram* may be the first indication of such a fistulous communication.

Diagnosis.—Cystoscopy will, as a rule, show only acute generalized cystitis with much œdema of the mucous membrane. This tends to obscure any view of the fistulous opening, which is usually found in the upper part of the posterior wall of the bladder towards its left side. Sigmoidoscopy is of little help, since the passage of the instrument is checked by the presence of the mass in the pelvis, and œdema of the mucous membrane tends to obscure any view of the fistulous opening. A barium enema may show the vesico-colic fistula.

To revert to causative factors. Harrison Cripps collected 63 cases, and ascribed their causes to: (1) Trauma. (2) Cancer. (3) Inflammation.

He stated that such fistulous communications were much more often due to inflammatory causes (presumably the modern diverticulitis which was unknown in 1888), and that prognosis by treatment was much better than in the case of cancerous growths. In two of his cases the condition was due to trauma, one following labour of four days' duration, and the other the result of impalation on a stake which traversed the bladder and rectum. Cancer was responsible for only nine cases.

Cripps laid stress on the fact that a fistula into the bladder seldom follows carcinoma of the rectum. An "inflammatory condition" accounted for 45 out of the total of 63 cases.

In 1884 Cripps reported 13 cases of imperforate anus. In 10 of these the patients died and post-mortem examination showed fistula between: rectum and prostate in six; rectum and bladder in three; distal end of the sigmoid and bladder in one.

Willan (*Brit. Med. Journ.*, 1933 (ii), 141) reported two cases of urinary calculus with ulceration into the rectum, and also a case of fistula resulting from carcinoma of the pelvic colon; this case was treated by resection and made a good recovery. He further reported a case of sacculitis of the pelvic colon with vesico-colic fistula; this also was treated by resection and made a good recovery. One case of carcinoma of the rectum with recto-vesical fistula was reported.

Higgins (*Journ. Urol.*, 1936, **36**, 694), stated that up to 1936, 548 examples of vesico-intestinal fistula had been collected from the literature. He gave an extensive ætiological table. His statistics show that the greater percentage of vesico-intestinal fistulæ result from diverticulitis, also that fistulæ following carcinoma of the rectum are not nearly so common as those following carcinoma of the pelvic colon. He states that a fistulous track may be a direct communication between the bowel and bladder, and that this occurs more often in cases of carcinoma, a long tortuous track being more often associated with an abscess between the bladder and bowel.

Lett (*Proc. Roy. Soc. Med.*, 1932, **25**, 1802) states that in 172 cases of diverticulitis admitted to the London Hospital during the ten years 1922–1931, there were only seven cases of vesico-colic fistula. There were three other cases admitted during this period, one secondary to carcinoma of the pelvic colon. The cause could not be determined in the other two. There was no X-ray evidence of diverticulitis.

Nitch quotes from the St. Thomas's Hospital records for a similar period. In 754 cases of carcinoma of the colon and rectum there were seven cases of vesico-colic fistula, whereas in 73 cases of diverticulitis a fistula was present in two cases.

At the Royal Free Hospital during the past seventeen years, only one case can be found in the records of vesico-colic fistula, and this was apparently due to diverticulitis.

At St. Mark's Hospital during the past ten years, there are records of seven cases : Three of vesico-colic fistula following diverticulitis of the colon ; two of vesico-colic fistula following carcinoma of the colon ; one of recto-vesical fistula following perineal prostatectomy ; one of recto-urethral fistula following prostatic abscess.

Treatment.—This resolves itself into colostomy for diverting the passage of fæces and, if necessary, a temporary suprapubic cystostomy.

In the majority of cases a transverse colostomy is advisable, since there is often very little loose colon above the lesion for making a left iliac-colostomy, and in cases of diverticulitis the descending and iliac portions of the colon are often markedly affected.

In cases of diverticulitis a well-fashioned colostomy with a good spur is usually sufficient to ensure healing of the fistula. This is not so, however, in cases of malignant disease, in which an attempt should be made to resect the affected portions of bowel and bladder as soon as the colostomy is functioning satisfactorily.

In cases of diverticulitis, symptoms usually disappear rapidly after a colostomy has been made, and the fistula closes in due course. One should therefore not be in a hurry to attack the actual lesion. If after an interval of from twelve to eighteen months the fistula has not closed, attempts should be made to suture the fistulous opening. This is, however, a difficult and dangerous operation, and one should hesitate to resort to it until all inflammation has subsided.

In conclusion, I have to thank my colleagues at St. Mark's Hospital for permission to quote their cases, and my thanks are also due to Mr. Nevin, Resident Surgical Officer at St. Mark's Hospital, and to Miss D. J. K. Beck, Surgical Registrar at the Royal Free Hospital, for help in examining the notes.

Dr. Cuthbert Dukes : No one can make any contribution to the pathology of urinary fistula without first paying tribute to Harrison Cripps. His book entitled " The Passage of Air and Fæces from the Urethra " was published in 1888. Until he undertook the special study of this subject he was under the impression that communication between the intestine and bladder was generally the result of malignant disease, but his investigations convinced him that entero-vesical fistulæ were far more commonly the result of " inflammatory mischief " than due to perforation from cancerous growth. The records he gives cover nearly two centuries, and stretch from the time when a general practitioner in Northampton claimed that communication between the intestine and bladder might be cured by a course of ass's milk and Bristol water, to cases successfully treated by modern methods.

Willan (1933), in a review of the subject forty-five years later, points out that Cripps makes no mention of diverticulitis as a cause of fistula, and suggests that 27 of the cases described under the heading of abscess, stricture, and ulcer, were probably a sequel to what we should now call diverticulitis. Willan described six cases met with in his own experience. Several other reviews of the subject have been published during the last few years.

Having paid my tribute to Harrison Cripps, I now turn to my own special contribution to this discussion on urinary fistula. As pathologist to St. Mark's Hospital for

Diseases of the Rectum, I have sometimes been asked to carry out laboratory tests to decide whether or not urine has found its way into the intestinal tract or is leaking from a perineal wound. As pathologist to St. Peter's Hospital for Stone and Diseases of the Urinary Organs, I have been asked similar questions when it has been suspected that the contents of the intestine were trespassing into the bladder. Most cases of urinary fistula can, of course, be recognized easily without the aid of laboratory tests, but there are occasions when these may provide important evidence, so I will give a brief description of the tests which are most likely to be useful—(1), in the detection of urine where it has no right to be, and (2), in the recognition of fæcal contamination.

(1) *The detection of urine.*—Tests for the detection of urine may be used to confirm the existence of a urinary fistula in wounds or suppurative lesions affecting the urinary organs. Also after the operation of transplantation of the ureter in carcinoma of the bladder, laboratory tests may show whether or not urine is being excreted with the intestinal contents.

The simplest method is to test for urea. The addition of a few cubic centimetres of freshly prepared alkaline hypobromite will result in a vigorous effervescence if urea is present. If this simple test is inconclusive, the best plan is to estimate the amount of urea in the material by the methods used for urine. Urea is normally present in the blood and in all the fluids of the body, except urine, to the extent of from 20 to 40 mgm. per 100 c.c. In urine the quantity of urea is from 1 to 2% or from 1,000 to 2,000 mgm. per 100 c.c. If the material to be examined contains more urea than is present in the patient's blood it is certain evidence of admixture with urine.

When only a drop or two of material is available for analysis the urease test will show whether or not urine is present. The ferment urease acts on urea, producing alkalinity due to ammonium carbonate. To carry out the test, add a few drops of phenol red to the material and then adjust the reaction till the fluid is just not red. Add urease, and if urea is present the fluid will turn red in a few minutes.

(2) *Recognition of fæcal contamination.*—When a fistula has developed between the intestine and the bladder the passage of air in the urethra may precede that of fæcal matter. At first the air is often so slight in quantity and so seldom passed that the patient himself has some doubt as to its occurrence. In these circumstances Cripps recommended that the patient should pass water while sitting in a hip bath. However, pneumaturia is not pathognomonic of fistula between the bladder and bowel because it may occur as the result of previous catheterization or be found in bladder infections associated with glycosuria.

When fæcal matter comes away with the urine in any considerable quantity there is no difficulty in recognizing it, but when it is small in amount, and mixed with the products of cystitis, it is not so easily identified. In these cases microscopic examination of the centrifuged deposit will generally clinch the diagnosis. The finding of fæcal débris and particles of undigested muscle and starch is sure evidence of the existence of a fistula between the intestine and urinary tract. If any doubt remains, the best plan is to carry out a bacteriological examination for the presence of spore-bearing anaerobic bacteria. These are always present in the intestine and almost never in the urinary tract (only in association with gas-gangrene infections). To carry out the test, a few c.c. of urine are heated at 60° C. for half an hour to kill off non-sporing bacteria, and then 1 c.c. is added to melted glucose agar in a deep glucose agar tube so as to provide an anaerobic culture. The tube is incubated overnight, and the presence of spore-bearing anaerobic bacteria is shown next day by the large quantities of gas formed within the medium.

These tests for the detection of urine and the recognition of fæcal contamination

are easily carried out. They are definite in their conclusions and sometimes provide evidence which would not be obtained in any other way.

REFERENCES

CRIPPS, HARRISON, "The Passage of Air and Fæces from the Urethra", London, 1888.
HIGGINS, C. C. (1936), *J. Urol.*, **36**, 694.
WILLAN, R. J. (1933), *Brit M. J.* (ii), 141.

Sir Hugh Devine said that the main type of urinary fistula in relation to the colon and rectum which had come under his consideration was one associated with diverticulitis. In many cases the fact that such a fistula had formed gave the medical attendants the impression that the patient was suffering from inoperable carcinoma.

An example of a particular case, which he would like to describe, would show the confusion which occurs in diagnosis, and also his methods of dealing with these cases.

The patient had been sent to him with the diagnosis of prostatic obstruction. This diagnosis was based on frequency of micturition and the presence of pyuria. The patient had not, however, any difficulty in micturating, nor were there any other typical symptoms, and there was no obvious cause for the cystitis to which the pyuria was supposed to be due. Painstaking cross-examination showed that, now and again, the patient passed the smallest quantity of air at the end of micturition. However, no trace of fæces could be found in the urine. A diagnosis of vesico-sigmoid fistula was made. The absence of fæces in the urine was subsequently shown to be due to the fact that the opening was valvular.

His operative method of dealing with this case was as follows: The distal colon was completely disconnected at the hepatic flexure by a type of colostomy which he had recently described in literature; thus the distal colon was completely excluded. At the same time an examination of the sigmoid was made. This showed that there was a large tumour connecting the sigmoid to the bladder, with a considerable amount of cellulitis of the sigmoid, extending from this tumour.

After two weeks in hospital the patient was sent home for six months, and instructed how to wash out the distal colon. (The separate opening into the distal colon had been so constructed that a stomach tube could be snugly fitted into it.) Because of the small disconnecting anus he was able to keep himself continent, and was thus able to go back to work.

At the second operation, after the lapse of six months, the sigmoid condition and the tumour had so far retrogressed that an anastomosis could be made in healthy tissues. The lower part of the sigmoid was removed and an end-to-end anastomosis made, and the opening of the bladder closed. The lumen of the sigmoid was found to be comparatively clean.

The main precaution, Sir Hugh Devine thought, was that adequate and prolonged drainage from the region of the anastomosis should be provided. This drainage was carried out as follows: Before the patient was placed in position for the operation the coccyx was removed through a small incision. It was then possible to introduce a tube through the abdominal wall, lead it down beside the anastomosis, and down through the opening made by the removal of the coccyx, thus providing a perineal and abdominal drainage. He then used the omentum to separate the anastomosis from the rest of the body cavity.

He found that even at the end of twelve days there was still a considerable amount of drainage. At the end of a fortnight the tube was removed. Three weeks after the operation, when saline was injected through the rectum, it was found that there

was still a leak in the anastomosis. Time was then allowed to elapse until the anastomosis was perfectly healed, when the fæcal stream was turned by crushing the spur.

The small colostomy, because of its smallness, was closed with the greatest ease.

He (the speaker) thought that the prolonged drainage as described was an essential part of an operation carried out under such adverse circumstances.

The President: These fistulæ may be divided into three groups: (1) Ureteric fistulæ, due to damage to one of the ureters during removal of the rectum or uterus. (2) Fistulæ between the colon and the bladder, due to diverticulitis or appendicitis. (3) Fistulæ between the urethra and rectum, or skin, caused by a prostatic abscess.

Ureteric fistulæ can only be dealt with by removal of the kidney, after making sure which ureter is damaged. When the injury to the ureter is discovered during the operation, transplantation of the ureter into the fundus of the bladder can be performed, or if this is impossible and there is good reason to believe that the kidney is healthy, the ureter can be tied and the corresponding kidney will stop secreting and will atrophy.

Fistulæ between the bladder and colon afford some of the most difficult problems in surgery. The method I have always adopted has been to perform a transverse colostomy and then to wait for a year—until all active inflammation has ceased, as far as possible, before attempting to resect the parts and close the opening in the bladder. As a rule the adhesions are so dense that the only way to separate the parts is to cut through the fibrous tissue with a knife or scissors. The damaged bowel is generally best resected and the ends joined up again. The hole in the bladder can be sewn up if healthy tissue is obtainable. As a rule one finds a hole in the middle of dense fibrous tissue which cannot be sewn up. I have found that such holes can be successfully closed with omental plugs, sewn over to keep them in position.

I had one case which I think must be unique. The patient was a man aged 33, who, as the result of a neglected appendix abscess, had suffered from a vesico-rectal fistula, which also communicated with the ileum. When I saw him he had a transverse colostomy. Urine escaped from both ends of the colostomy opening and from the rectum, and fæces passed through the urethra. What finally made him decide that he must have something done was that he found himself passing "raisins" through the urethra.

I made a complete transverse incision across the abdomen, from one iliac crest to the other, and divided both recti muscles; this gave free exposure to the whole of the pelvis. There was a mass of fibrous tissue, the size of a man's fist, consisting of the cæcum, ascending colon, and over a foot of ileum, attached to the fundus of the bladder, which I cut completely away. The end of the ileum was joined to the transverse colon and there were then two large holes, one in the rectum and one in the bladder. Both of them were plugged with omentum and sewn over, and the bladder was drained by a tied-in catheter and a tube through the abdominal wall. The patient made a perfect recovery, and a few months later I closed the colostomy. He is now, some years later, quite fit and well.

The cases which have caused me most trouble have been those in which the fistula was due to a prostatic abscess and the urethra or bladder communicated with the rectum or with a perineal fistula. I should like to know what is the best way of tackling such cases, as I have not been very successful in getting the fistulæ to close.

Mr. C. I. Naunton Morgan said he agreed with Sir Hugh Devine that it was important—after anastomosis of the sigmoid to the rectum, following exclusion of the colon—to close the preliminary transverse colostomy within a month or six weeks, since the suture line tended to become constricted.

An unusual accident which produced a urinary fistula with the colon was described—a uretero-colic fistula on the left side following the insertion of an enterotome to establish continuity of the bowel. This fistula healed spontaneously, and six months afterwards cystoscopy with ureteric catheterization showed the ureter to be completely healed.

A specimen was shown which illustrated that sometimes, when conditions were favourable in a thin person, a vesico-colic fistula due to diverticulitis could be dealt with without preliminary colostomy. This case had been treated by partial cystectomy, temporary suprapubic drainage, and extraperitoneal resection of the sigmoid colon.

Section of Comparative Medicine

President—S. P. Bedson, M.D., F.R.S.

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DISCUSSION ON IMMUNITY TO ANIMAL PARASITES

Metazoal Immunity

By N. Hamilton Fairley, M.D.

The subject of metazoal immunity is expanding rapidly ; an extensive review of the work which has appeared since Taliaferro's classical monograph (1929) can be found in Culbertson's recent papers (1938) on the immunology of helminthic infections.

Animals, including man, present the phenomena of both natural and acquired immunity to helminthic infestation. Concerning the mechanism of natural immunity we know little, but once the tissues have been invaded, a cellulo-humoral reaction ensues in response to the presence of the invading helminths, or their glandular secretions, metabolic products, ova or embryos. The cellular reaction is typified by the presence of leucocytes, including eosinophiles, round cells, macrophages, and foreign-body giant cells. According to Taliaferro (1934) the polymorphonuclear leucocytes and the macrophages are most directly involved ; the macrophages apparently bear the brunt of the work while the smaller cells of the lymphoid-monocytoid series form a mesenchymal reservoir from which macrophages can be developed.

In somatic helminthiasis, precipitin and complement-fixing antibodies have frequently been demonstrated in the serum, and allergic reactions shown by intradermal tests with extracts of the invading helminths, larvæ, or embryos. Allergic syndromes detrimental to the host may develop in both myiasis and helminthiasis.

The parenteral injections of embryonic and worm extracts may result in the appearance of circulating antibody, and in some instances in the development of a greater or lesser degree of resistance to infection as well.

When injected into a susceptible host, sera from infected animals have occasionally been shown to confer a variable degree of protection against infection, but the protective properties have not yet been identified with precipitin or complement-fixing antibody. The so-called " protective antibodies " often appear to be developed against the immature rather than the adult parasite, and to be of the nature of " growth-inhibiting " substances which may lead to abnormal development, stunting of growth and, in the mature female, to inhibition of the reproductive functions with consequent decrease or disappearance of ova altogether. Similar effects may be noted in certain hosts which enjoy a natural immunity to the helminths concerned.

I.—Natural Immunity

The capacity of helminths to invade successfully the tissues of man, and of different species of animals, varies widely. Some helminths, like the adult *Tænia saginata*, are restricted to one species of host ; others, like *Schistosoma japonicum*, may affect many mammalian species ; others again, like *Trichinella spiralis*, may

implicate not only many different mammals, but birds as well. Species resistance is generally absolute and lifelong, but sometimes it may be relative and only acquired as the host grows older. Such host factors as age, dietary, and a decreased hæmoglobin content of the blood, or massive infection and enhanced virulence on the part of the parasite, may determine successful invasion and infestation, especially in the case of an imperfectly adjusted species of helminth.

The mechanism which determines species immunity is very incompletely understood. Possible factors will be briefly considered :—

(*a*) *Secretions inhibiting or preventing helminthic invasion.*—In the case of the monogenetic trematode, *Epibdella melleni*, which is ectoparasitic on the skin and eyes of certain marine fishes, Nigrelli (1935) has shown that the mucus from a naturally resistant species, such as the dogfish, kills the parasites *in vitro* in from three to five hours, whereas mucus from a susceptible species, such as the pompano, exerts no deleterious influence. Here immunity is, at least in part, determined by the mucoid secretion of the host.

Hydrochloric acid in concentrations normally present in the gastric juice rapidly destroys bilharzia cercariæ. In ruminants of the family Bovidæ, such as goats, cattle, and water-buffalo, hydrochloric acid is absent from the rumen, reticulum, and omasum, and the chance of alimentary infection is thereby increased. Fairley and Jasudasan (1930) showed that goats could be invariably infected by introducing cercariæ of *S. spindale* via a stomach tube. These animals dislike water except for drinking purposes, and in them infection via the upper alimentary tract is probably the rule.

Berberian (1936) recently found that at 37° C. the intestinal juices of sheep, cattle, and man, digested viable hydatid scolices, while those of the dog and cat failed to do so. These experimental findings may explain the basis of the natural immunity enjoyed by the herbivora and man to the adult stage of *Echinococcus granulosa*, and the susceptibility of other species of animals like the dog and cat, which act as definitive hosts.

(*b*) *Factors inimical to the parasite after invasion has occurred.*—These may include antagonistic cellular reactions at the site of invasion or in the internal organs, a failure of the host tissues to act as suitable pabulum for the growing parasite, or the presence of growth-inhibiting substances or natural protective antibodies in the blood or body fluids. Fairley, Mackie, and Jasudasan (1930), showed that freshly shed cercariæ of the cattle schistosome, *Schistosoma spindale*, survived much longer in the serum of a susceptible host like the goat than in *Macacus rhesus* monkeys, which were naturally immune. More recently Culbertson (1936) has reported that the fresh serum of certain vertebrates is lethal to cercariæ, and concluded that this may constitute the basis of the species immunity which they manifest.

It is not always easy to determine where natural immunity ends and acquired immunity begins, in different hosts. The following observations by Fairley, Mackie and Jasudasan (1930) on different species of animals exposed to infection with the cattle schistosome, *Schistosoma spindale*, illustrate the complexity of the subject. Even in a susceptible animal like the goat, only a small proportion of viable cercariæ applied to the skin attain maturity, and, of those which do, only a proportion subsequently survive.

During the early phases of the disease in hyperinfected goats, schistosomes were not confined to the portal system, and worms were unexpectedly found to be dying. Later, a biological equilibrium was established between the parasites and the definitive host. The surviving worms were then strictly limited to their ordinary habitat—the portal and mesenteric veins—and verminous phlebitis and death of schistosomes were no longer observed. Death of the parasites was accompanied and followed by a rapid rise in the antibody content of the serum, which not uncommonly, at this stage, fixed 30 to 60 M.H.D. of complement in the presence of cercarial antigen, but there

was no actual proof that this antibody was responsible for the early death of the worms.

Monkeys of the species *Macacus sinicus* developed positive complement-fixation reactions in the second week after exposure to bilharzial cercariæ, but after three months the reaction became negative, and at autopsy no worms, ova, or pathological lesions were demonstrable. But when infected monkeys were killed in the early stages and at short intervals, it was found that developing schistosomes (schistosomulæ), though extremely active and plentiful in the portal system until the eleventh day, disappeared during the next ten days, the animals undergoing spontaneous cure. The phenomenon was attributed either to an obscure antischistosomula immunity response or to some inherent unsuitability of the blood of this host for the developing schistosomulæ. Observations in a further series of experimentally reinfected monkeys suggested that following spontaneous recovery the immunizing mechanism was temporarily speeded up, since the invading schistosomulæ failed to develop and survive for even the usual eleven-day period following re-exposure.

Guinea-pigs were also exposed to infection with *S. spindale*, by employing viable cercariæ derived from many different snails. Hepatic lesions characterized by verminous phlebitis and thrombosis were constantly demonstrated, but only male worms developed normally and attained maturity. As both male and female cercariæ were used, the phenomenon of exclusive male survival was shown to depend on some host factor inimical to the female worm and not on unisexual infection as had previously been thought.

II.—Acquired Immunity

Immunity following infection may be local or general. A few examples may be cited.

(1) *Local immunity.*—Perhaps the best example of acquired local immunity is that described by Blacklock and Gordon (1927) with the myiasis-producing Tumbu-fly, *Cordylobia anthropophaga*. They showed that after primary penetration of larvæ into the skin, or after inoculation with emulsions of larvæ, guinea-pigs acquired a local skin immunity which tended to extend gradually from the primary focus to areas of skin which had not been the site of invasion by parasites or of previous inoculation. The local immunity persisted in skin transplanted from an immune to a non-immune animal. In the case of the monogenetic trematode, *Epibdella melleni*, Jahn and Kuhn (1932) also noted that after certain fish had recovered there was local immunity in the area of the skin formerly implicated, and that when reinfection occurred, it affected a fresh area of the dermis. Nigrelli (1935) failed to transfer passively any acquired immunity to reinfection, while attempts at active immunization also gave negative results. The case for the development of a local immunity was, therefore, a strong one.

Chandler (1935) holds that the immunity reactions to parasites in the alimentary canal are local and not dependent on humoral antibodies, his conclusions being mainly based on observations on the trichostrongyloid nematode, *Nippostrongylus muris*, in albino rats. He failed to confer passive immunity by injections of immune serum, and found in parabiotic twins that no immunity to reinfection was conferred on the previously uninfected twin. He concluded that acquired immunity was a property of the intestinal mucosa, probably due to the inhibition by anti-enzymes of the enzymes which were the parasites' normal means of assimilating host protein. Inhibition of egg production in female parasites, and stunting of growth in immature parasites resulted. Chandler (1936) also found that in rats immunized with dead larvæ, the female worms that developed were reduced in size, many were immature, and the eggs per gramme of fæces were greatly reduced. When transferred to non-immune rats the parasites attained maturity and produced eggs normally. The anti-

enzymes therefore had caused no permanent damage to the developing parasites. Sarles and Taliaferro (1936), on the other hand, reported the passive transfer of immunity, together with the finding of a precipitate around and in the gut of worms, in sections of the skin and lungs of immune rats. They conclude that the immunity to *N. muris* is essentially a local immunity in strategically placed organs such as the skin, lungs, and intestine, but that it has to a large extent an antibody basis. The stunting of growth is attributed, not to an antibody which kills the worms, but to an ablastin (reproduction-inhibiting antibody) such as has been described by Taliaferro in the rat, against *Trypanosoma lewisi*.

(2) *General immunity.*—After parasites have actually invaded the tissues or blood-vessels of the host, definite evidence of an acquired immunity or enhanced refractiveness to reinfection is sometimes forthcoming. Furthermore, in some parenteral infections, the immunity can be passively transferred in the serum, proving that it is blood-borne and dependent on humoral antibodies.

Acquired immunity is perhaps best illustrated by reference to the larval cestodes. Miller (1930 and 1931) found that when cysts of *Cysticercus fasciolaris* were present in the liver of naturally or artificially infected rats, such animals became immune to subsequent infection with oncospheres fed through a stomach tube. In albino rats, artificially immunized by injections of the adult worm extract, oncospheres failed to develop normally. After surgical excision of the cysts, Miller and Massie (1932) showed that this acquired immunity lasted sixty days or more, the development of the oncospheres fed during this period being almost completely inhibited. Passive transfer of immunity was also demonstrated by Miller (1932) in non-infected rats which had received an intraperitoneal injection of serum from either infected or artificially immunized rats, at the same time as the oncospheres were fed, but if the injection was postponed for nine days or longer, larval development was little interfered with.

Time unfortunately does not permit a review of the work on artificial immunization against cestodes and nematodes by the injection of parasitic extracts, or of the various factors such as unbalanced diet, vitamin deficiency, intercurrent disease, anæmia, and pregnancy, which may decrease host resistance to infection or upset the biological equilibrium between host and parasite.

III.—Antibody Response and Laboratory Diagnosis

The intestinal helminths do not give rise to precipitin or complement-fixation antibody unless, like *Ascaris lumbricoides*, they, at some stage in their life-history, invade the tissues of the host. Eosinophilia and dermal sensitivity to parasitic extracts may, however, develop in an exclusively intestinal infection. In somatic helminthiasis, on the other hand, circulating antibody is often demonstrable by the complement-fixation and precipitin tests. Subsequent remarks will be mainly confined to those reactions which have been found of value in the routine investigation of diseases such as echinococcosis, schistosomiasis, filariasis, and trichiniasis.

(*a*) *Complement-fixation reaction.*—Ghedini (1906) first applied the Bordet-Gengou reaction to the diagnosis of helminthic diseases, and since then considerable progress has been made in reactions of this type. As a rule alcoholic extracts of the desiccated powdered worms or their embryos prove more satisfactory antigens than aqueous-saline extracts for complement-fixation work, since they are sterile and retain their antigenic properties for many years if stored in an ice-chest. The antigenic factor is thermostable, acetone-insoluble, and alcohol-soluble, while alcoholic extracts containing it may fail to give chemical reactions for protein.

Hydatid disease.—In hydatid disease two antigens are available for serological work—the cyst fluid used first by Ghedini (1906) and scolex extract introduced by Fairley (1922). The two antigens yield comparable results. Though alcoholic scolex antigen keeps for years, it very occasionally yields positive reactions where

hydatid infestation can be excluded, and for this reason hydatid fluid is probably preferable if a fresh supply, uncontaminated by bacteria, can be obtained each week. K. D. Fairley and Williams (1930), in a series of 147 hydatid cases, reported that only about one in three cases with uncomplicated or degenerated cysts presented a positive reaction, whereas in ruptured or suppurative cysts positive results were almost always obtained. The reaction is essentially of a group nature, and sera from patients with cysticercosis will react with either cyst fluid or scolex antigen.

Schistosomiasis.—The complement-fixation reaction in Japanese schistosomiasis was investigated in man by Yoshimato (1910), using an alcoholic extract of adult schistosomes (*Schistosoma japonicum*) as antigen. Cross reactions were noted with Wassermann-positive syphilitic sera. In Egypt, Fairley (1919) failed to obtain a satisfactory antigen from adult schistosomes for the diagnosis of the vesical (*S. hæmatobium*) and intestinal (*S. mansoni*) types of the disease, but found that an alcoholic extract of the livers of snails infected with bilharzia cercariæ showed marked antigenic properties. A high percentage of positive reactions was recorded in bilharzia infestations in man as well as in experimentally infected monkeys. During the first two years 93·2% of patients infested with either or both species of parasite yielded positive results, while in more chronic cases 74·2% were positive. In a consecutive series of 44 syphilitics with positive Wassermann reactions all the bilharzia complement-fixation reactions were negative.

The discovery of cercarial antigens was of some biological interest, since it was the first specific antigen obtained from an invertebrate intermediary host which reacted with the serum of a vertebrate definitive host. Extracts prepared from normal snail liver, or livers infected with non-bilharzia cercariæ, proved non-antigenic. The reaction was found to be of group nature, since sera from either the intestinal or vesical types of the disease reacted with antigen prepared from any of the bilharzia-infected molluscs found in Egypt. Later, when working with certain cattle schistosomes, Fairley (1925 and 1933) found that extracts of snails' livers (*Planorbis exustus*) infected with cercariæ of *S. spindale* constituted potent antigens for the detection of infestations with *S. spindale*, *S. indicum*, *S. mattheei*, and *S. bovis* in goats, as well as *S. japonicum*, *S. hæmatobium*, and *S. mansoni*, in man. The group nature of this reaction for mammalian schistosomiasis was thus demonstrated.

Filariasis.—A new complement-fixation reaction in filarial disease was described by Fairley (1931), using an alcohol-soluble extract of the dog filaria, *Dirofilaria immitis*, as antigen. Eleven out of 70 sera tested yielded positive reactions, and, of these, seven were actively infested with *Loa loa* and came from the West Coast of Africa. The four remaining cases were regarded as active or latent infections with *Filaria bancrofti*. Lloyd and Chandra (1933) examined 89 cases, using extracts of *D. immitis* as antigen. They obtained positive results in *F. bancrofti* and guinea-worm disease, but not in other diseases. In a more recent unpublished series examined by the writer the reaction has proved most satisfactory in calabar swelling (*Loa loa*), where 28 out of 30 consecutive cases (i.e. 93%) gave positive reactions. Much less satisfactory results were obtained in *Filaria bancrofti* infestation, in which the test proved of no practical value. The sera of 1,056 patients, in whom there was no evidence of filariasis or guinea-worm disease, yielded positive reactions in only two instances. In many cases with a history suggestive of calabar swelling, embryos are not demonstrable in the noon-day blood, and here a positive complement-fixation reaction, especially if associated with an eosinophilia and a positive skin test, entirely favours the diagnosis of *Loa loa*.

(*b*) *Precipitin tests.*—Precipitin tests have been described in a number of helminthic diseases, but do not appear to have met with the same practical success in serological diagnosis as complement-fixation reactions.

Hydatid.—Fleig and Lisbonne (1907) first demonstrated a specific precipitin in the serum of a patient with hydatid disease and in the sera of animals immunized with

hydatid products, and Welch and Chapman (1908) reported favourable results in man. The test has now generally been discarded in favour of the complement-fixation reaction, owing to the difficulty in reading weak reactions with a fine precipitate and failure to make the test a quantitative one.

Schistosomiasis.—Miyaji and Imai (1928) reported positive precipitin reactions in rabbits and dogs experimentally infected with *S. japonicum*, using as antigen a saline extract of the adult parasites. In man, Taliaferro, Hoffman and Cook (1928) reported positive results with extracts prepared from the dried powdered livers of snails infected with cercariæ of *S. mansoni* and extracts of the cercariæ free from liver substance. The technique adopted was that of the ring test.

Trichiniasis.—Bachman (1928) followed Strobel's technique of digesting trichinous meat and obtained live trichinæ which were subsequently dried, powdered, and extracted with ether; the ether-insoluble residue was subsequently hydrolysed in 0·1% HCl and its pH adjusted. By means of the ring test he demonstrated precipitin in the rabbit's serum from the thirtieth day onwards. These results have generally been confirmed in animals and extended to man by other observers, but the clinical value of the test is limited by the lag in the appearance of demonstrable antibody in the circulating blood. Bachman (1928) also described a skin test in experimentally infected animals. In man the immediate type of reaction is obtained during the second week of infection. When combined, the tests constitute a definite aid to diagnosis in doubtful cases.

(c) *Intradermal tests.*—Intradermal tests reveal hypersensitiveness to helminthic extracts or parasitic cyst fluid, and following their intradermal inoculation, both immediate and delayed reactions may be observed. The immediate reaction is characterized by diffuse erythema and a rapidly increasing wheal with peripheral pseudopodial-like projections, reaching a maximal size in about thirty minutes. If too concentrated a solution be injected in a hypersensitive person, generalized urticaria with or without alarming anaphylactic features may rapidly ensue. The delayed reaction generally develops some hours after the immediate reaction has faded, and is characterized by an extensive erythema with a definite margin, and a diffuse tight swelling of the subcutaneous tissues. Though the reaction occasionally disappears within twelve hours, it is generally present for twenty-four hours and may last two or three days. In the severest reactions vesiculation at the site of the original injection follows. Hypersensitivity can be passively transferred by the injection of serum, using the Prausnitz-Küster technique.

The immediate reaction is best regarded as an antigen-antibody union within the cell itself, with histamine-like effects (Dale) or the actual liberation of "H substance" (Lewis) leading to reflex arteriolar flare and œdema from increased permeability of the vascular endothelium. The delayed reaction is dependent on a more slowly developing œdema of the subcutaneous tissues with reflex dilatation of the peripheral arterioles.

Casoni (1911), who first described a skin test in hydatid disease, injected cyst fluid deep into the subcutaneous tissues, reading the results next day. Naturally his observations only concerned the delayed reaction. It was many years later that Ithurrat (1923) made the injection intradermally and stressed the importance of the immediate wheal. Both phases of the reaction are now recognized as important, and when they both appear indicate a marked degree of hypersensitivity.

Ransom, Harrison and Couch (1924) carried out extensive investigations on the skin reactions in ascariasis, but failed to determine whether the allergen was a protein. Cross reactions in other nematode infestations limit the practical value of the test.

Fülleborn (1925), employing the scratch test, reported immediate reactions in patients infected with *Strongyloides intestinalis* when tested with strongyloid extracts. He emphasized that positive reactions indicated past as well as present infection.

A skin test characterized by immediate and delayed phases was described by Fairley and Williams (1927) in schistosomiasis of man, using filtered saline extracts of *S. spindale* as antigen. The group nature of this reaction was demonstrated.

In infections with *Filaria bancrofti*, Taliaferro and Hoffman (1930) reported an intradermal reaction, employing extracts of *Dirofilaria immitis* as antigen. Fairley (1931) independently confirmed these findings and found that equally intense reactions were elicited in *Loa loa* infestation. Here the delayed reaction developed earlier, large blubber-like swellings appearing within four hours and closely resembling in appearance the calabar swelling itself.

IV.—Allergic Phenomena

Time will not permit a survey of this important field, but mention may be made of the hay-fever-like syndromes in Ascaris-sensitive individuals, the frequency of urticaria and eosinophilia, and the asthmatic features which occasionally develop in the course of helminthic infestations. Perhaps the best example of local allergy is the calabar swelling, which results from an allergic reaction in the subcutaneous tissues to secretions of adult *Loa loa*. In this disease generalized urticaria and even asthma may occur, and Murgatroyd and the writer have succeeded in desensitizing patients presenting these features by a course of injections with Dirofilaria extract. One such patient has remained entirely free from urticaria and asthma for over two years. In other patients, the calabar swellings have decreased in both frequency and intensity as a result of such injections, but in no instance have they altogether ceased to appear.

All degrees of anaphylactic shock and even rapid death may follow the escape of hydatid fluid into a vein or serous cavity. Here, as in the anaphylactic reaction induced in skin tests by an overdosage of helminthic extract, subcutaneous injections of adrenaline are indicated. Apart from the helminths there are many examples of allergic reactions induced by metazoa. The immediate and delayed local type of skin reaction may follow insect bites, and occasionally generalized anaphylaxis may supervene as in individuals hypersensitive to bee- or wasp-stings. But the best example is the syndrome studied by Hadwen and Bruce (1917) in sheep and cattle infected with the larvæ of certain warble flies (*Hypoderma bovis*, *Hypoderma lineatum*, and *Œstrus ovis*). The warble larvæ inhabit the subcutaneous tissues and sensitivity to larval products develops. Spontaneous or artificial rupture of warble nodules produced marked allergic manifestations, while the injection of larval extracts intravenously was rapidly followed by salivation, lacrimation, dyspnœa, asthma, cardiovascular shock, cyanosis, staggering gait, convulsions, and even death. Autopsy revealed an absence of coagulation of the blood, dilatation of the right heart, and hæmorrhages into the mucous membranes of the lungs and alimentary tract.

REFERENCES

Bachman, G. W. (1928), *J. Prev. Med.*, **2**, 35 and 169.
Berberian, D. A. (1936), *J. Helminthol.*, **14**, 21.
Blacklock, D. B., and Gordon, R. M. (1927), *Ann. Trop. Med.*, **17**, 443.
Casoni, T. (1911), *Folia clin., chim. et micr.*, **4**.
Chandler, A. C. (1935), *Am. J. Hyg.*, **22**, 167.
Id. (1936), *ibid.*, **23**, 46; **24**, 129.
Culbertson, J. T. (1936), *J. Parasitol.*, **21**, 433.
Id. (1938), *Arch. Path.*, **25**, 85 and 256.
Fairley, N. H. (1919), *J. Roy. Army M. Corps*, **32**, 449.
Id. (1922), *Med. J. Australia*, **1**, 341.
Id. (1925), *J. Path. and Bact.*, **28**, 591.
Id. (1931), *Trans. Roy. Soc. Trop. Med. and Hyg.*, **24**, 635.
Id. (1933), *J. Helminthology*, **11**, 181.
Fairley, N. H., and Jasudasan, F. (1930), *Indian Med. Res. Mem.*, No. 17, 11.
Fairley, N. H., Mackie, F. P., and Jasudasan, F. (1930), *Indian Med. Res. Mem.*, No. 17, 17-68.
Fairley, N. H., and Williams, F. E. (1927), *Med. J. Australia*, **2**, 811.
Fairley, K. D., and Williams, F. E. (1930), *J. Coll. Surg. Australia*, **2**, 317.
Fleig, C., and Lisbonne, M. (1907), *Compt. rend. Soc. de biol.*, **62**, 1198.
Fülleborn, F. (1925), *Klin. Wchnschr.*, **4**, 1709.
Ghedini, G. (1906), *Gaz. degli Ospedali e delle Cliniche*, **27**, 1616; *ibid.*, **28**, 153.
Hadwen, S., and Bruce, E. A. (1917), *J. Am. Vet. M. A.*, **51**, 15.

ITHURRAT, F. (1923), *Compt. rend. Soc. de biol.*, **88**, 348.
JAHN, T. L., and KUHN, L. R. (1932), *Biol. Bull.*, **62**, 89.
LLOYD, R. B., and CHANDRA, S. N. (1933), *Indian J. M. Research*, **20**, 1197.
MILLER, H. M. (1930), *Proc. Soc. Exper. Biol. and Med.*, **27**, 926.
Id. (1931), *ibid.*, **28**, 467, 884.
Id. (1932), *ibid.*, **29**, 1124; **30**, 82.
MILLER, H. M., and MASSIE, E. (1932), *J. Prev. Med.*, **6**, 31.
MIYAJI, S., and IMAI, B. (1928), *Centralbl. f. Bakt.*, **106**, 237.
NIGRELLI, R. F. (1935), *J. Parasitol.*, **21**, 438.
RANSOM, B. H., HARRISON, W. T., and COUCH, J. F. (1924), *J. Agric. Res.*, **28**, 577.
SARLES, M. P., and TALIAFERRO, W. H. (1936), *J. Infect. Dis.*, **59**, 207.
TALIAFERRO, W. H. (1929), *Immun. Parasit. Inf.*, New York. The Century Co.
Id. (1934), *J. Parasitol.*, **20**, 149.
TALIAFERRO, W. H., and HOFFMAN, W. A. (1930), *J. Prev. Med.*, **4**, 261.
TALIAFERRO, W. H., HOFFMAN, W. A., and COOK, D. H. (1928), *J. Prev. Med.*, **2**, 395.
WELCH, D. A., and CHAPMAN, H. G. (1908), *Lancet* (i), 1338.
YOSHIMATO, M. (1910), *Ztschr. f. Immunitätsforsch. u. exper. Therap.*, **5**, 438.

Immunity or Tolerance in Malarial Infections

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So much work has been done on this subject during recent years that it is not possible to give more than a very brief and general summary of the more salient points, in a discussion of this nature.

Malaria is a disease in which the case mortality, among adults at least, is usually relatively low. What generally happens in the absence of treatment is that the clinical attacks of the disease proceed eventually to spontaneous recovery, with a diminution of the parasite prevalence in the blood. There is, however, a great tendency for the parasites to increase again at a later date, giving rise to clinical relapses of the disease. This sequence of events shows that the host develops some immunity, temporarily at least, if he manages to survive the acute initial attacks of the infection. The rate of development of this immunity has been found to vary with (*a*) the species and strain of Plasmodium responsible for the infection, and (*b*) the degree of natural or acquired resistance possessed by the host at the time.

Two different factors appear to be involved in this immunity: (*a*) An antiparasitic element, whereby the parasites are kept at such a low level that few or no clinical manifestations are developed, and (*b*) an antitoxic one, whereby the "toxins"[2] produced are wholly or partly neutralized. The evidence at present available indicates that both these factors are closely associated with the activities of the macrophage or reticulo-endothelial system.

Factors influencing the Multiplication and Pathogenicity of Malarial Parasites in the Vertebrate Host

In the absence of therapeutic intervention, the host has two methods of attack upon the malarial parasite and its toxins: (*a*) A cellular one, and (*b*) a humoral one. These two factors are closely associated and act in combination. Their activities have been summarized briefly in Table I.

Cellular factors.—The cellular factor in the destruction of malarial parasites is the phagocytic activity of the macrophage system. In the early stages of a primary infection, the natural phagocytic activity of these cells comes into action in a non-specific manner and is very sluggish. The host then reacts to the infection by an increase in the number of these cells.

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[2] These bodies are purely hypothetical. No information is available as to their exact nature.

If the host survives long enough, this sluggish *non-specific* activity of the increased number of cells becomes changed into a very active *specific* phagocytosis. This results in a diminution in the number of parasites and a disappearance of the clinical manifestations, either temporarily or permanently. This specific activity is almost certainly stimulated by the humoral factors mentioned below.

Humoral factors.—Although we are still very uncertain as to the exact nature of these elements, yet there is much evidence to show that they exist.

In natural immunity or tolerance, probably one of the chief factors concerned is an inherent unsuitability of the body tissues to the multiplication or survival of the parasites. This seems to be completely non-specific, but in the case of acquired immunity there is almost certainly a development of specific antibodies. It has been found that, although the macrophage system may be highly stimulated and hypertrophied, yet it is relatively ineffective in controlling a severe attack of malaria in the absence of a specific defence element.

Experimental work on human and simian malaria has shown that, from an immunological point of view, each species of Plasmodium appears to be made up of two or more different strains, each with different antigenic properties. The specific

TABLE I.—MECHANISM OF PROTECTION AGAINST THE INVASION OF THE MALARIAL PARASITE AND AGAINST ITS PATHOGENIC EFFECTS.

(*a*) Against parasitic invasion	(1) *Cellular Factors* (reticulo-endothelial system). (i) Natural non-specific phagocytic activity of the reticulo-endothelial cells, which is rapidly followed by (ii) Great increase in the number of these cells, with the acquisition of (iii) Increased specific phagocytic activity of the individual cells due to humoral factors (?) either (*a*) the specific sensitization of the reticulo-endothelial cells, or (*b*) the effects of specific lysins or opsonins developed against the parasites. (2) *Humoral Factors* (nature doubtful). (i) Inherent unsuitability of the body tissues to the multiplication or survival of the parasites. (ii) Development of specific antibodies causing either (*a*) Destruction or increased susceptibility of the parasites, or (*b*) Increased specific activity of the reticulo-endothelial cells.
(*b*) Against pathogenic effects of infection	(iii) "Antitoxins."

defence element can only be developed as the result of an infection, and is only highly effective against a strain of Plasmodium having the same antigenic properties as that responsible for the previous infection. The antibodies are probably produced by the macrophage system as a result of the stimulation of ingested parasites acting as a specific antigen.

The specific humoral factor apparently acts in combination with the macrophages, and produces its effects either by (*a*) a specific sensitization of these cells whereby their phagocytic properties become very active, or (*b*) some specific action on the parasites rendering them more readily destroyed by the macrophages. The latter element may be a lysin, but seems more probably something in the nature of an opsonin.

There is also considerable evidence to show that "antitoxic" substances are probably produced by the body in its fight against malarial infection. This is suggested by the fact that, in the earlier stages of an acute infection, a much smaller number of parasites causes a more severe reaction than does an even greater number at a later date when tolerance has developed. It has also been reported recently that a certain degree of passive immunity can be transferred by the injection of serum from an immune subject.

The Development of Immunity or Tolerance in Malarial Infections

An attempt has been made in Table II to summarize the relative effects of the various factors in the defence mechanism at different stages of a malarial infection.

The reaction of the host to infection depends primarily upon his degree of natural resistance to the multiplication of the parasites in his tissues, and to the pathogenic effects caused by the surviving organisms. Should the invasion be successful, the after-results are determined by the rapidity of development, the intensity, and the duration of the specific resistance which the host acquires as the result of his infection. These results may be influenced, of course, by the virulence of the strain of parasite introduced, and by the occurrence of therapeutic intervention.

TABLE II.—THE DEVELOPMENT OF IMMUNITY OR TOLERANCE IN MALARIA.

Type of Immunity or Tolerance	Mechanism of Protection: Antiparasitic (Offensive against invasion of parasites) — Macrophage system	Mechanism of Protection: Antiparasitic (Offensive against invasion of parasites) — "Antibodies"	Mechanism of Protection: Antitoxic (Defensive against effects of invasion) — "Antibodies"	Rate of mobilization of the specific protective mechanism or the duration of its action
Natural	+ or + → ++	++ (?) or + → +++	+++ (?) or + → +++	Already mobilized, or very rapidly mobilized
Acquired				
A. *Active*				
(1) Developing, in acute primary infections	+ → +++	+ − → +++	+ − → +++	Relatively slowly mobilized; rate varying with the type of parasite
(2) Concomitant, in chronic infections	+++	++ or +++	++ or +++	Already almost completely mobilized
(3) Superinfections				
(i) With new species	+++	+ − → +++	+ − → +++	Probably more rapidly mobilized than normal
(ii) With same species				
(*a*) Homologous strain	+++	+++	+++	Already specifically mobilized
(*b*) Heterologous strain	+++	+ → +++	+ → +++	More rapidly mobilized than normal
(4) Residual, in cured infections	+++ → +	+++ → ++ or +++ → + or +++ → + −	+++ → ++ or +++ → + or +++ → + −	Rate of loss seems to vary with duration of infection, and with species and strain of parasite
B. *Passive* (?)	+	+++ (?) → + −	+++ (?) → + −	Quickly lost, if present

Natural Resistance or Immunity

Some hosts appear to have a complete resistance to infection with certain species of Plasmodium, more especially those derived from hosts belonging to a different order, family, or even genus.

The so-called natural immunity in malaria may be of two types: (*a*) A complete resistance of the host to the development of infection, i.e. a true, complete, or absolute, *immunity*, and (*b*) an incomplete resistance to the invasion of the parasites. In the latter case, although the parasites gain a footing in the body they produce few or no clinical manifestations, i.e. a natural *tolerance* of the infection (malarial infection without malarial disease).

Some animals appear naturally to be completely resistant to infection with the human species of malarial parasite. In man, however, there is probably very seldom, or never, a complete natural immunity to the acquisition of infection by any of the human malarial parasites. The cases of absolute immunity reported are probably merely cases in which the infection acquired has been followed by so few pathogenic symptoms that it has escaped notice.

Natural tolerance may be the result of destruction of parasites by the non-specific defence mechanism of the host, or of the power of the body to neutralize the toxins,

or of an inherent insusceptibility of the host to the effects of the latter. Such tolerance has been found to be present in varying degree among a large proportion of the indigenous inhabitants of highly malarious areas. It appears to be due to a weeding-out of the more susceptible units by death in early life and so the eventual production of a more resistant race. These people seem to possess not only a resistance to the effects of infection but also the power to develop this rapidly to a very high and lasting degree. The antitoxic element appears to enter largely into this tolerance, for infected persons may often be seen with a high parasite prevalence but with few or no symptoms.

Acquired Immunity or Tolerance

The acquired immunity is mainly of an active nature, but recently some evidence has been forthcoming that a certain degree of passive immunity may also be transmissible.

Active acquired immunity.—The degree and rapidity with which this develops and the part played by the different defence factors, vary with the previous history of the host in respect of malarial infection, and probably also to some extent with his natural powers of resistance.

In acute primary attacks there is a rapid mobilization of the non-specific phagocytic mechanism. If the patient survives, there is a less rapid formation of the specific antiparasitic antibodies followed by the development of specific antitoxins. The rate at which these specific elements are developed varies with the species, or even with the strain, of Plasmodium responsible for the infection.

If the host does not succumb in the acute initial stages of the infection, or a radical cure, either natural or therapeutic, occur, a chronic or latent infection of varying duration tends to develop. During this stage, the specific defence mechanism keeps the parasites at a relatively low level and clinical manifestations are slight or absent. Although this tolerance lasts as long as the infection survives in the host, its efficacy may be occasionally broken temporarily by the occurrence of relapses. This type of *concomitant tolerance* is often referred to as *premunition*. During its continuance it is probably maintained at a high level by periodical, specific antigenic stimulation, occurring when young parasites or parasitic metabolic products are released into the blood-stream at each schizogonic division. It can be broken down completely by splenectomy, whereby the major portion of the hypertrophied and sensitized macrophage system is removed, and probably also the major source of the specific antibodies.

When a host possessing a high degree of tolerance to a species of Plasmodium is superinfected with another species, the defence mechanism is usually ineffective in preventing the development of an acute attack of the disease due to the new parasite, i.e. there is no *cross-immunity*. The specific immunity against the new invader will probably be developed more rapidly than in the case of a host who has not previously suffered from malaria, because the macrophage system is already non-specifically mobilized for defence purposes.

When a premunized host is superinfected with the same strain of parasite as that responsible for its latent infection, little apparent effect is produced on the course of the infection. This is very different from what is seen when the superinfection is due to a heterologous strain of parasite, even although the host already possesses a high degree of homologous immunity. The new parasites multiply rapidly and clinical manifestations occur, which may be almost as severe as those seen in the original primary attack. The attack may, however, be slightly less severe than normal. This is probably because of the hypertrophy of the macrophage system present and because all strains of the same species of parasite possibly possess some small amount of common antigenic property.

When an infection has been completely eliminated, either by natural or therapeutic means, a certain degree of *residual immunity* remains. If the infection has been cut short very early in its course by therapeutic measures, the immunity acquired seldom reaches a high level and usually disappears comparatively rapidly. When, however, the infection has continued for a considerable period, weeks or months, the long and repeated antigenic stimulation appears to produce an immunity which is of a much more lasting character after the eradication of the infection. This is especially so when the host has been subjected to multiple superinfections with the same species of Plasmodium. The residual immunity found after infection with *P. falciparum* appears to be more fleeting than that observed after *P. vivax*, while that after *P. ovale* seems to be very lasting.

Passive immunity.—It has been suggested by some workers that a certain amount of passive immunity may be transmitted from a malarious mother to her offspring, more especially *in utero*. The evidence for this is as yet very inconclusive.

Many attempts have been made in the past to transmit a passive immunity in malaria, but with little success. More recently, however, by the injection of very large amounts of serum from a host with a high degree of acquired immunity, it has been reported that in certain cases of avian, simian, and human, malaria, the infection in a new host can be definitely modified. This suggests that, if antibodies are present, their concentration in the peripheral blood must be very weak.

Protozoan Diseases of Stock

By U. F. Richardson, M.R.C.V.S., B.Sc.

My interest has chiefly been in protozoan diseases of stock.

In areas in which diseases due to the intracellular protozoa (Coccidia, Babesia, Theileria) occur, young animals contract an infection that is often symptomless, and remain immune throughout life. Relapses occur in exceptional circumstances, but in general the presence of these parasites would not be noticed if imported animals did not contract disease. In the exceptional cases there may be a considerable mortality of young stock. In Britain, as far as my observations have gone, every flock of fowls harbours Coccidia, and oocysts corresponding to those described for all six species are usually present. Every sheep I have examined—most of them butcher's animals—showed coccidial infection. 90% of rabbits also harbour infection. It is believed that in early youth these animals contract mild symptomless infections before they are exposed to gross contamination. Susceptible adult animals introduced into such areas contract acute disease and may die.

According to the early work of Tyzzer (1932) and other American investigators, fowls infected with coccidia and protected from reinfection become free from the parasites and are then liable to become infected again. If exposure to infection is maintained, superinfection and reinfection occur, but after a time complete immunity is established. How long such immunity will persist was not determined.

Biester and Murray (1930), working with coccidia of pigs, reached similar conclusions, but added that immunity persisted only for a few weeks.

More recently Tyzzer (1936) has modified his original views and says that some fowls may maintain infection indefinitely. I have commonly found infection in fowls which have been kept in batteries for two and three years, and, when each bird is kept in a separate cage on wire floors, it is difficult to believe that reinfection could occur regularly enough for the parasites to persist so long, if they were not capable of surviving indefinitely in their hosts.

There appears to be little evidence that in fowls or sheep the immunity to Coccidia can be broken down, but in cattle in India and Kenya it is said that rinderpest immunization will cause a relapse to coccidiosis. From Tyzzer's observations on

fowls there seems little doubt that superinfection can occur, and it is possible that such relapses in cattle are in fact reinfections, the rinderpest immunization reducing the resistance to reinfection rather than to the strain persisting in the host.

Short (1938) and others, working with Babesia of dogs in India, say that superinfection can rarely be accomplished. But if it can occur at all it would probably be difficult to detect, and it may be more common than is supposed.

Again, rinderpest immunization is said to cause a breakdown to Babesia infection in cattle, but modern methods of freeing the virus used in immunization from piroplasms has greatly reduced the number of such accidents. Again it seems that superinfection was the most important factor.

By treatment of dogs, Short was able to eliminate the persisting piroplasmal infection, and in one case set up a fatal reinfection within about three weeks. The evidence, though still rather meagre, seems to suggest that infection with these intracellular parasites may persist indefinitely, and superinfection may occur, but the host is immune to the pathogenic action of the parasite unless the latter has been completely eliminated. Immunity is then lost in a few weeks. The pathogenic action in these cases seems to depend on cell destruction. Tyzzer was unable to detect circulating antibodies, but the cells of immune birds resisted sporozoite invasion and the invading sporozoites withered and degenerated.

A possible explanation is that we must look on such diseases as diseases of the cells attacked rather than of the host. The sporozoites of Coccidia, in attacking the intestinal epithelium, fail to establish themselves in some cells, which become immune. The cells in which attack is successful die and are replaced by new cells, some of which may resist attack, and the number of immune cells tends to increase. Normally, new susceptible cells are formed quickly enough to maintain infection. Rinderpest, which causes a great destruction of intestinal epithelial cells, would thus destroy those immune to Coccidia, and since the new cells formed would have no immunity, the Coccidia would find practically virgin epithelium to reinfect.

Trypanosome infections.—In their natural hosts the initial infection is often nonclinical. The blood of cattle or dogs may be swarming with trypanosomes and the animals be in apparently excellent health. According to Taliaferro's (1932) work on *T. lewisi* in rats, the host reaction consists in the production of two antibodies, one inhibiting multiplication and the other causing lysis. Apparently the trypanosome responds by the formation of relapse strains which are not susceptible to these antibodies, and infection is characterized by a succession of waves of lysis and multiplication which may continue indefinitely. We cannot say there is any immunity to the pathogenic action. An infection may be apparently benign at the start, the host remaining in good health for years, then for no apparent reason the host may develop clinical symptoms and, if untreated, die without any marked increase in the numbers of the parasites. Since antiparasitic treatment leads to recovery it seems that the parasites themselves are responsible for such relapses.

We know that infection may persist unnoticed for very long periods. There is a record of one man in whom clinical disease did not develop till fifteen years after his return to Europe. Cattle and camels have been kept under observation and trypanosomes have only been occasionally detected in their blood for periods up to three years, although the species concerned was normally highly pathogenic (*T. congolense* and *T. evansi*).

It is believed that game in a "fly belt" develop quite a serviceable immunity by the process of infection in youth followed by repeated reinfection. Schilling's (1935) experiment in Tanganyika, in which calves were infected and then exposed in a tsetse area, will reach a very interesting stage when the animals become mature.

Cattle exposed in Uganda to *G. palpalis* develop a double infection with *T. brucei* and *T. vivax* and suffer a loss of condition and a mortality of about 10%. After a year or more of exposure no further trypanosome infection can be detected, and

their condition often becomes excellent. In a very limited number of experiments blood from such animals proved non-infective on subinoculation and they resisted reinoculation with *T. vivax*. One does not claim that they were free from infection, which is extremely difficult to prove, but *T. vivax* is usually easily reinoculable to an apparently recovered animal, so it would seem they had more than the ordinary immunity of the once-infected beast.

In dealing with trypanosome immunity the greatest difficulty is to decide whether a given animal is free from residual infection or not. In the case of the more pathogenic trypanosomes like *T. congolense* it seems that ordinarily superinfection cannot be produced, so that if reinoculation is successful it has been assumed that recovery has occurred. But Parkin and Hornby (1930) were able to cause superinfection with a strain of trypanosome from another area. After apparently successful treatment reinfection is usually obtainable, and such tests as the mercuric chloride test in camels and the complement-fixation test in horses give negative results. The use of such tests may give us more reliable information as to whether superinfection is readily obtainable and whether sterile immunity ever occurs.

At the present time there seems to be a possibility that solid immunity may be reached through recovery followed by repeated reinfection in youth. Such a process might produce a lysin which was capable of dealing with any relapse strains before the animal was too mature to make an efficient resistance. It would make a considerable difference to Africa if stock could be acclimatized in tsetse areas. As has been pointed out by Duke (1936) and others, one of the great causes of human disease in such areas is the low standard of living in them, and a supply of milk, butter, meat, and fats, might make them more suitable for prosperous settlements which would, in time, displace the tsetse.

REFERENCES

Tyzzer (1922), *Am. J. Hyg.*, **15**, 319.
Biester and Murray (1930), *J. Am. Vet. M. A.*, **76**, 624.
Tyzzer (1936), 2nd Internat. Congress for Microbiol. Abstr., 183.
Short (1938), *Indian J. M. Research*, **25**, 763.
Taliaferro (1932), *Am. J. Hyg.*, **16**, 32.
Schilling (1935), *Ztschr. f. Immunitätsforsch. u. exper. Therap.*, **85**, 513.
Parkin and Hornby (1930), 16th Rep. Dir. Vet. Services and Anim. Indust., S. Africa, 11.
Duke (1936), *Epidemiol. Rep. League of Nations*, **15**, 187.

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Experimental Investigations on the Relationship of the Anterior Hypophysis to Diabetes Mellitus

By F. G. YOUNG, Ph.D.

SEVEN or eight years ago our theories of the cause of diabetes appeared to be much more complete and satisfactory than they are to-day. There seemed to be no serious doubt that the cause of the majority of cases of diabetes mellitus was a deficient secretion of the islets of Langerhans of the pancreas. There was some indication that the pituitary gland might sometimes be involved, but it was generally agreed that the posterior rather than the anterior lobe of this gland was to be considered.

During the years 1930–31 the Argentinian investigator B. A. Houssay and his colleagues announced some results of investigations on the relationship of the pituitary gland to experimental diabetes which were of fundamental importance, and although their significance was not at once generally recognized, Houssay's researches have undoubtedly provided the main stimulus for the vast amount of research in this field which has taken place during the last few years. Houssay's first important discovery in this connexion was the observation that in a variety of species removal of the pituitary gland greatly diminished the severity of the symptoms of diabetes which normally follow extirpation of the pancreas (*see* Houssay and Biasotti [1931], and Houssay [1936] for summaries of the results of these extensive researches). It was also shown that implantation or injection of anterior (but not of posterior) pituitary material into a hypophysectomized-depancreatized animal resulted in a great increase in the severity of the diabetic symptoms. Subsequently Houssay and a number of other investigators almost simultaneously observed that the daily administration to intact normal animals of extracts of the anterior pituitary lobe might result in the appearance of the symptoms of diabetes which, however, disappeared the cessation of daily injections. All these results combined to suggest that hyperfunction of the anterior pituitary lobe might sometimes provide a cause of the symptoms of diabetes mellitus.

Before I go further I should perhaps define the manner in which I propose to use the words "diabetes" and "diabetogenic". A condition in which the symptoms hyperglycæmia, glycosuria, ketonuria, polydipsia, and polyuria, are exhibited will be termed "diabetes", and any agent which provokes the appearance of all these symptoms simultaneously will be described as "diabetogenic". The use of the term "diabetes mellitus" will be restricted to a description of diabetes in human beings. It should be pointed out that the majority of the investigations considered will be concerned with the artificial production of diabetes in animals, and there is no proof that the results of these researches will directly throw light on the ætiology of clinical diabetes mellitus, though it seems possible that they may ultimately do so.

I propose to consider first some investigations on the experimental production of a diabetic condition by anterior lobe treatment, then to discuss the action of anterior pituitary extracts on particular aspects of carbohydrate metabolism, and finally to discuss, very briefly, the possible mechanism whereby these pituitary extracts exert their diabetogenic action. It will be possible to consider only a small fraction of the total number of papers published in each field, and I hope I may be forgiven if I tend to consider the results of investigations in which I have been concerned, perhaps to the exclusion of the results of more important or interesting researches.

THE PRODUCTION OF A DIABETIC CONDITION BY THE ADMINISTRATION OF AN ANTERIOR PITUITARY EXTRACT.

Dogs are by far the most satisfactory animals to use for the demonstration of the diabetogenic activity of anterior pituitary extracts in intact animals (cf. Young, 1938 A). Cats and rabbits exhibit less striking and consistent results, while rats and mice are comparatively insensitive. Extracts with diabetogenic activity are only slowly effective and it is only after two or three daily injections that hyperglycæmia and glycosuria appear.

If a dog is given a daily intraperitoneal injection of a suitable amount of a crude saline extract of fresh anterior pituitary gland there is usually no obvious result until the third or fourth day, when hyperglycæmia is exhibited, the urine volume increases, and sugar and ketone excretion begins. If the daily administration of the same amount of extract is continued for from seven to ten days, the glycosuria and ketonuria (but often not the polyuria) usually subside and finally disappear in spite of the continued daily injections. If the amount of extract injected daily is then suitably increased, hyperglycæmia, glycosuria, and ketonuria, reappear, only to disappear again with continued daily administration of the diabetogenic extract (Young, 1936 A and C, 1938 A and B). The disappearance of the symptoms, followed by a reappearance, with increase in the amount of extract injected daily, may occur a number of times, and has been observed in rabbits and cats as well as in dogs. The discovery of this phenomenon suggested that if the amount of extract injected was increased suitably at intervals of three days (fig. 1), the animal should remain continuously diabetic during the period of injections, and this proved to be so (Young, 1937 D). An important question then became evident: If the amount of extract injected daily were increased to a very high level, would the dog become completely resistant to the diabetogenic action of the extract, or would it lose its power of becoming resistant? The latter proved to be the answer, and all except one of the animals investigated have been found to be incapable of resisting the diabetogenic action of a daily dose of crude extract equivalent to 25 grm. of fresh tissue. Moreover, in these animals, when the daily injections of extract ceased, the diabetic condition continued and had apparently become permanent (Young, 1937 D). This was of interest for the reason that treatment with anterior pituitary extract appeared to provide a means of producing a permanently diabetic condition without recourse to surgical interference with the pancreas. To date, of six dogs treated with suitably large doses of extract only one has failed to become permanently diabetic (Young, 1938 D). The remaining five have shown no sign of recovery from the diabetic condition, but their behaviour has differed in a number of respects from that of depancreatized dogs. The most important difference is that our dogs are able to survive for long periods, perhaps indefinitely, without insulin treatment. Up to the present two dogs have lived for ten months and another for six months without exhibiting any indication of the necessity of insulin treatment. Another point in which our dogs differ from depancreatized dogs is that in the former the loss of body-weight is not excessive, provided that sufficient food is given, and for long periods a normal body-weight may be maintained. This is in spite of the fact that these dogs give the classic symptoms of being able to oxidize only a small part of ingested carbohydrate. Metabolic studies on these dogs have been carried out in collaboration with Mr. H. P. Marks (*see* Marks and Young, 1938 B), and Table I gives an indication of the type of data obtained, and the influence of alterations in the composition of the diet. From this table it will be seen that when the dog is receiving a protein diet the D/N ratio indicates, according to the general interpretation, maximal formation (and excretion) of sugar from protein. Ketone excretion is much less on a carbohydrate diet than on a régime of protein food. Body-weight can be maintained, or even gained, on the high protein diet if sufficient food is ingested, in marked contrast to a depancreatized dog, and, for a short time at least, weight may

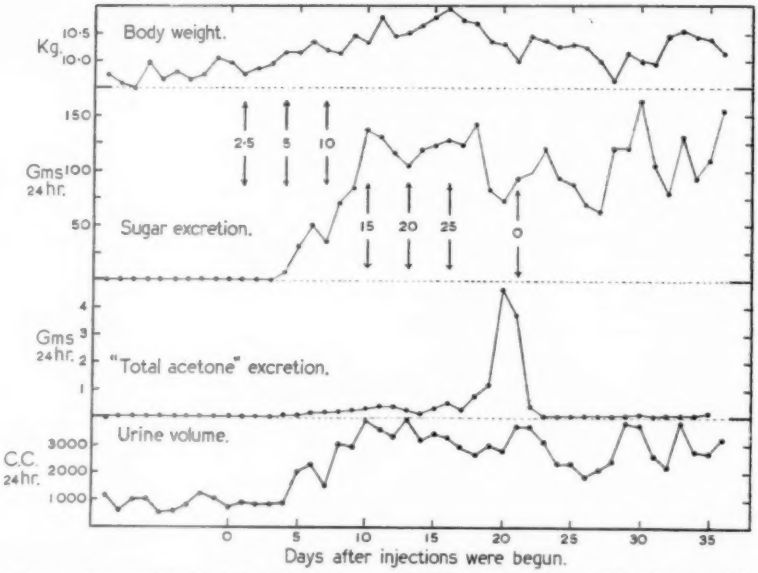

FIG. 1.—Dog receiving daily injections of a crude anterior lobe extract. The figures on the arrows give the weight, in grm., of fresh ox anterior lobe used to prepare the amount of extract injected daily, from the day indicated by the arrow, onwards. Injections ceased on the day indicated by the arrow carrying 0. The ketonuria, which fell to a low level following the cessation of injections, rose later.

not be lost on the high fat diet. As would be expected, the animal loses weight rapidly when receiving the carbohydrate diet.

If 50 grm. of glucose is given to one of these dogs when it is fasting, or receiving a protein diet, sometimes, though not always, the whole of the sugar may apparently be excreted (fig. 2), the sugar tolerance curve being of a diabetic type (fig. 3) and often having a terminal rise. On the other hand, if the dog is fed on a high carbohydrate diet, 10% or so of the carbohydrate ingested daily may be retained (Table I), so there

TABLE I.—SUMMARY OF DATA RELATING TO A DOG OF ABOUT 10 KILOS MADE PERMANENTLY DIABETIC BY INJECTION OF ANTERIOR PITUITARY EXTRACT

Diet	Amount of food consumed daily	Sugar excretion, grm./day	D/N (corrected)	"Total acetone" excretion, grm./day	Blood-sugar after 24 hr. fast mgm./100 c.c.	Approximate percentage of calories in diet retained
Protein	300-1500 grm. of raw meat	50-250	3/1-4/1	1·0-13·0	250-450	55
Carbohydrate	200-300 grm. of biscuit	140-220	—	0·0- 0·5	350-500	10
Fat	100-400 grm. of beef suet	1-15	—	0·1- 3·5	—	> 90
Fasting (48 hours)	—	About 15	2·5/1	About 0·6	About 290	—

can be little doubt that these dogs are able to utilize a small amount of sugar. As might be expected, their respiratory quotient is abnormally low and, so far, no rise has been detected after the ingestion of 50 grm. of glucose.

Two of these dogs have received insulin treatment for short periods as an experimental procedure. Each required about 60 units a day of insulin to render the urine almost free from sugar and ketones when it was receiving a liberal meat diet. It should be mentioned that none of the dogs has exhibited symptoms indicative of deficiency of the external secretion of the pancreas.

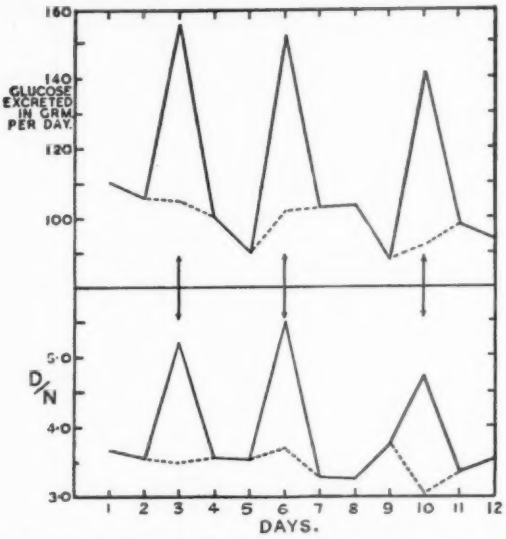

FIG. 2.—Dog made permanently diabetic by anterior lobe treatment. On the days indicated by each arrow 50 grm. of glucose were added to the daily ration of meat. The solid lines indicate the sugar excretions and D/N ratios actually observed, while the dotted lines show the values obtained when 50 grm. was subtracted from the observed sugar excretion. The results show that, in these experiments, the extra 50 grm. of glucose were apparently quantitatively excreted. In other experiments on the same dog the glucose recoveries were sometimes not as complete as in those illustrated above.

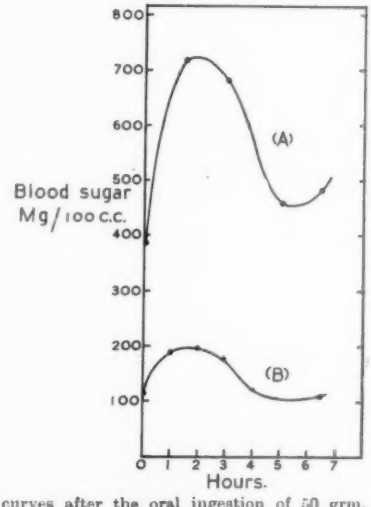

FIG. 3.—Blood-sugar curves after the oral ingestion of 50 grm. of glucose in the dog. *Curve A:* Average results for three experiments on different dogs made diabetic by treatment with pituitary extract. N.B.—The rise of blood-sugar between five and six-and-a-half hours was present in all three instances. *Curve B:* Average result for two experiments on normal dogs.

Examination of specimen of pancreatic tissue from two dogs which had been diabetic for ten months has revealed changes in the islets of Langerhans (Richardson and Young, 1938). In one instance the islets were completely hyalinized and contained no detectable normal islet tissue. The pancreatic tissue of the other dog, which incidentally has given the lowest D/N ratios and glucose recoveries of those so far examined, contained a few normal islets, but most of the islets examined showed varying grades of depletion of the cytoplasmic granules of the beta cells. In both instances there was an extensive fatty infiltration of the pancreatic duct epithelium. The other endocrine glands of these dogs showed no striking abnormality, but it may be mentioned that in one instance there appeared to be an unusually large number of vesicles containing colloid in the pars intermedia of the pituitary gland.

Dr. C. H. Best has informed me that he and Dr. J. Campbell have recently succeeded in confirming these observations on the production of a permanent diabetes in dogs by anterior lobe treatment, in the University of Toronto. Dr. Best and Dr. Campbell have also observed changes in the histological picture of the islets of Langerhans of one of these dogs.

Before I pass on to consider other aspects of the action of anterior pituitary extracts on carbohydrate metabolism, I will mention four possible methods of explaining the difference between the behaviour of these permanently diabetic dogs and that of depancreatized dogs.

(1) The diabetic condition of these dogs is due to a deficiency of insulin, but the islets can still secrete an amount of insulin which, if suitably administered to a completely depancreatized dog, would be sufficient to maintain life.

(2) The diabetic condition is due to deficiency of insulin, which would lead to fatal inanition in the depancreatized dog, owing to the absence of pancreatic enzymes. The subnormal digestive powers of the depancreatized dog would not permit of the ingestion of sufficient non-carbohydrate food to cover the urinary loss of carbohydrate, but our diabetic dogs are able to obtain sufficient calories by the ingestion of large amounts of non-carbohydrate food.

(3) The diabetic condition is due to the action of an extra-pancreatic factor, which stimulates an overproduction of sugar in the body. An attempted compensation by the pancreatic islets would involve increased secretion of insulin, which might lead to a picture of exhaustion or degeneration in the islet cells.

(4) The acinar tissue of the pancreas plays a hitherto unsuspected role in the metabolism of carbohydrate.

One cannot do more than mention these possibilities at the present stage, but I would like to point out that the second of these suggested explanations carries the implication that the old belief that the complete oxidation of fat requires the co-operative oxidation of carbohydrate is incorrect. Unfortunately, it is not possible to discuss this point here (see, however, Young, 1936 A).

The discussion of the mechanism of the diabetogenic action of anterior lobe extracts will involve a consideration of the action of anterior pituitary substances on some general aspects of carbohydrate metabolism and the action of insulin in particular.

The Influence of the Anterior Pituitary Gland on the Action of Insulin.

Insulin has a number of different but related actions on the metabolism of carbohydrate, and the influence of extracts of the anterior pituitary gland on a number of these will be considered separately.

(*a*) *The general hypoglycæmic action of insulin.*—As long ago as 1925 Houssay and Magenta found that hypophysectomy markedly increases the sensitivity of an animal to the hypoglycæmic action of insulin, but it is only within the last few years that the influence of anterior lobe extracts on the insulin sensitivity of hypophysectomized

and of normal animals has been investigated. Cope and Marks (1934) found that the daily administration of a crude saline extract of anterior lobe to a rabbit induced a chronic insensitivity to the hypoglycæmic action of insulin, so that the intravenous administration of 2 units had no observable effect on the blood-sugar level. It should be stressed that in the experiments of Cope and Marks, as in others which will be considered shortly, the administration of the anterior pituitary extract had, in most instances, no significant effect of its own on the blood-sugar level, and, further, that the response to the injection of insulin was not determined until some hours (sometimes a day) had elapsed since the last administration of extract. The abolition of the hypoglycæmic effect was therefore not the result of an antagonistic hyperglycæmic action of an extract administered with the insulin. Cope and Marks found that the hyperglycæmic action of subcutaneously administered adrenaline was abnormally great in the pituitary-injected rabbits, and explained the abolition of insulin hypoglycæmia in these animals on the basis of the supposition that, under the influence of the extract, the liver glycogen stores were rendered excessively susceptible to the mobilizing action of adrenaline, so that any tendency to hypoglycæmia was prevented by the rapid formation of glucose from the glycogen of the liver.

In an attempt to purify the pituitary substance responsible for these effects, I found that the active principle was present in preparations of the so-called lactogenic hormone—prolactin (Young, 1936 B)—though later investigations showed that the active substance was not identical with prolactin, or with the gonadotropic or thyrotropic hormones (Young, 1937 A ; 1938 B). Since the early observations were made, a number of other investigators have also found that preparations of prolactin may exert an influence on carbohydrate metabolism (*see* Riddle *et al.*, 1937) although it is not yet generally recognized that a contaminant of prolactin, and not prolactin itself, is probably the active principle. I have suggested (Young, 1936 A) that for the purpose of convenience the active principle should be provisionally named the " glycotropic " pituitary factor, without prejudicing the question of whether or not it is identical with any of the known pituitary substances. The investigations to which I shall now refer were carried out with preparations of the glycotropic factor which were rich in prolactin but almost free from the thyrotropic and gonadotropic hormones.

If two suitable injections of glycotropic factor are given sixteen hours apart to a fasting intact rabbit, the hypoglycæmic action of 2 units of crystalline insulin, administered intravenously some hours after the last pituitary injection, is entirely abolished (fig. 4). Similar, but less striking results can be demonstrated when the glycotropic factor is administered to the hypophysectomized rabbit. The hyperglycæmic response to subcutaneously or intravenously administered adrenaline may be greatly increased under these conditions. All these responses can be demonstrated in rabbits in which the blood level has not been significantly affected by the anterior pituitary injections alone.

As Dr. H. P. Himsworth was interested in the action of the glycotropic factor, I gave him some of our preparations, and he and Dr. McN. Scott (1938 B) were able to show that these were effective in rabbits from which the thyroids or the adrenal glands had been removed. The latter observation is of great importance, as it shows that the glycotropic factor does not exert its action through the medium of adrenaline secreted by the adrenal glands.

Himsworth and Scott (1938 B) also investigated the influence of the glycotropic factor on the action of insulin in the liverless rabbit. Removal of the liver induces a rapid fall of the blood-sugar, which is accelerated by insulin, but in rabbits which had received injections of the glycotropic factor this accelerating action of insulin was absent.

De Wesselow and Griffiths (1936) have found that the injection into young rabbits of plasma from a certain type of human diabetic patient can induce a diminished

sensitivity to the hypoglycæmic action of insulin, similar to that produced by the administration of the glycotropic factor. Plasma from normal subjects, and from a different type of diabetic patient, was inactive in this respect. It seems possible, therefore, that the plasma of a particular type of diabetic patient may contain an abnormal amount of the glycotropic factor, which suggests that, in some instances at least, clinical diabetes may be of pituitary origin.

Collip (1934) has shown that if an animal receives daily injections of a preparation of the anterior pituitary thyrotropic substance, the serum of the injected animal may, after many weeks' injection, possess the ability to neutralize the thyrotropic action of the extract. The administration of the antiserum to a normal animal can render it insensitive to the physiological action of the hormone of "antigenic" pituitary preparation. The similar formation of antisera in response to injections of other anterior lobe hormones has since been studied by a number of investigators. If, in some instances, human diabetes is associated with excessive production of the pituitary glycotropic substance, the results of the administration to such cases of

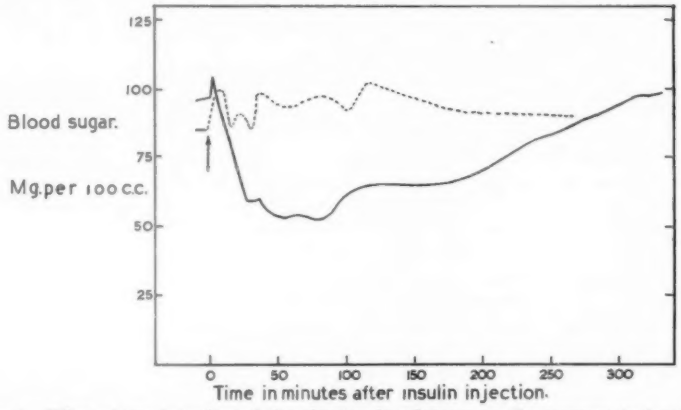

FIG. 4.—Effect of two injections of the glycotropic substance on the response to 2 units of intravenously administered crystalline insulin in the rabbit.
Solid curve—Reponse before pituitary injections.
Dotted curve—Response four and a half hours after the second injection of pituitary extract.

antiserum to the glycotropic factor would be of interest. By the prolonged daily administration to monkeys and rabbits of preparations of prolactin, rich in glycotropic substance but containing no detectable thyrotropic or gonadotropic hormones, it was possible to produce an antiserum active in neutralizing the action of prolactin in the pigeon crop-gland, but this serum exhibited no consistent antiglycotropic activity (Young, 1938 c). These experiments do not prove that the glycotropic substance is incapable of evoking an antiserum, and further investigation of this point seems desirable, if only because such an antiserum might have some clinical value, as well as physiological interest.

(*b*) *The action of insulin on glycogen storage.*—In 1926, Best, Dale, Hoet, and Marks showed that in the eviscerated spinal cat, insulin promotes the formation of muscle glycogen from glucose in the blood. Recently Marks (1936) has demonstrated that this aspect of the action of insulin is inhibited in animals which have received injections of the glycotropic factor.

Although in most instances insulin decreases the liver glycogen level, in the young rabbit—as Goldblatt (1929) first showed—the administration of 1 unit of insulin substantially increases the liver glycogen content. Marks and I (Marks and Young, 1938 A) have recently found that in young rabbits treated with relatively purified

preparations of the glycotropic factor, this rise under the influence of insulin does not occur. The fact that the initial (i.e. pre-insulin treatment) level of liver glycogen in the animals receiving glycotropic factor was considerably higher than that of untreated animals (*vide infra*) may have been a contributory cause to this failure to respond to insulin.

(*c*) *Other observations.*—The discovery that the glycotropic substance can inhibit the action of insulin in the peripheral tissues (Marks, 1936; Himsworth and Scott, 1938 B) provided a simple explanation of the manner in which dietary changes may influence insulin sensitivity, and Himsworth and Scott (1938 A) have recently obtained definite evidence that the influence of changes of diet on the action of insulin is mediated by the anterior pituitary gland.

The results considered so far indicate that, in the rabbit, the glycotropic factor can abolish the hypoglycæmic and glycogen-storing actions of insulin, without causing a significant rise of blood-sugar level. The mechanism of action is not certain, but it seems clear that the adrenal medulla does not play an intermediary role. The fact that an animal may become completely resistant to the hypoglycæmic action of exogenous insulin without itself becoming diabetic is a curious one, and requires further investigation.

Preparations of prolactin rich in the glycotropic factor are not diabetogenic in the dog (Young, 1938 B). On the other hand, the daily administration of anterior lobe extracts possessing glycotropic activity, but containing no detectable prolactin (i.e. the pigeon crop-gland stimulating substance), induces diabetes in dogs (Young, 1938 B). Although the glycotropic factor is therefore not diabetogenic *per se* in the dog, it is possible that this factor is one constituent of a diabetogenic complex.

The Action of Anterior Pituitary Extracts on the Islet Tissue of the Pancreas.

In 1933, Anselmino, Herold and Hoffmann claimed that the administration of an anterior pituitary extract to rats results, in a few days, in a substantial increase in the number and size of the islets of Langerhans of the pancreas. This increase was assessed solely on the basis of the histological appearance of isolated or serial sections of the pancreas, a method which is obviously open to objections. It is not surprising therefore that there has been much disagreement with regard to the question of this alleged " pancreotropic " action of anterior lobe extract (for references, see Richardson and Young, 1937). Richardson and Young (1937), using a tedious but objective method for the quantitative determination of the pancreatic islet tissue in the rat, found that the amount of islet tissue in animals which had received daily injections of a crude saline extract of fresh ox anterior lobe for from two to three weeks was about twice that of control animals. Anselmino *et al.* used an aqueous extract of acetone-dried anterior lobe, and in our experiments this type of extract was without significant effect on the *amount* of islet tissue, although some pancreases exhibited giant islets and a histological picture which has been interpreted by many workers as indicative of proliferative activity of the islet tissue.

It seemed of significance that the type of extract which produced diabetes in dogs was that which we found to be effective in increasing the amount of islet tissue in rats, and the possibility was visualized that the islet hypertrophy was a compensatory response to a diabetic condition induced by injections of the extract, prompter and more effective in the rat than in the dog. However, the blood-sugar levels of groups of rats receiving this type of extract were within normal limits, and, although the possibility could not be ruled out entirely, it seemed improbable that the islet hypertrophy in the rat could be merely a compensatory response to the diabetogenic action of the extract.

These results with the rat suggested the necessity of seeking indications of islet hypertrophy in pancreatic tissue from dogs which were receiving daily injections of a diabetogenic pituitary extract. Pancreas from two such animals was examined by

Richardson and Young (1938), who found indications of unusual mitotic activity in the islet cells. Hydropic changes were present in other cells. Mitosis is rarely seen in the pancreatic islets of the normal dog, and mitotic figures were sufficiently common in the islets of these animals to suggest that an unusual rate of proliferation of the islet tissue was occurring. In the absence of quantitative data on the amount of islet tissue in these pancreases, it was, of course, impossible to determine whether or not any significant increase in the amount of islet tissue had occurred. It should be pointed out that there is, as yet, no evidence that any islet tissue formed under the influence of anterior pituitary extracts is capable of secreting insulin. If, however, one response of the dog's pancreas to diabetogenic extracts is a relatively slow functional proliferation of the islet tissue, then the ability of a dog to become resistant to the diabetogenic action of a small daily dose of extract (*vide supra*) would find an explanation.

We do not know whether a saline extract of fresh anterior lobe contains a specific substance causing islet-tissue hypertrophy, or whether this activity is associated with one of the recognized pituitary hormones. Richardson and Young (1937) failed to find evidence that the increase of islet tissue in rats was merely a compensatory response to the diabetogenic activity of the crude extract, but until the "pancreotropic substance" has been separated from other pituitary factors—if indeed this is possible—its individuality must remain in doubt. It is clear, however, that should it prove possible to prepare a "pancreotropic substance" free from other undesirable anterior pituitary factors, the investigation of the clinical uses of such a preparation might yield results of great interest.

The Influence of Anterior Pituitary Extracts on the Glycogen Stores during a Fast.

Russell and Bennett (1936) and Fisher, Russell and Cori (1936) found that hypophysectomized rats lose liver and muscle glycogen at an abnormally high rate during a short fast, and that the abnormal loss of muscle glycogen—but not of liver glycogen—could be prevented by treatment with a crude anterior pituitary extract during the fast. Subsequently I found (Young, 1937 B) that adult rabbits receiving injections of the glycotropic factor during a short period of fasting possessed, at the end of the fast, substantially more liver and muscle glycogen than did control animals. Further investigations on this point were carried out by Marks and Young (1938 A) using young rabbits. It was found that as well as containing a greater percentage of glycogen, the livers of young rabbits receiving injections of anterior lobe extract during a short fast were substantially heavier than those of control animals, the increase in weight of the livers being proportional to the increase in glycogen content (fig. 5). The total amount of glycogen in the livers of the injected young rabbits was therefore much greater than that of control animals, in one instance being eleven times as great. The greater liver weight was due to the presence of extra total water, fat, and glycogen, in the livers of the animals receiving anterior lobe treatment. Best and Campbell (1936) first clearly showed that the action of anterior lobe extracts may lead to an increase in liver-fat content, and it is interesting to find in our experiments that a rise of liver fat may be accompanied by the accumulation of abnormal amounts of liver glycogen.

The source of the extra liver glycogen in our experiments is not at all clear. As the glycogen level of the muscles is also raised, muscle glycogen cannot provide the source. Russell and Bennett (1936) believe that in their experiments the greater glycogen content of the pituitary injected, as compared with that in uninjected fasting hypophysectomized rats, was due to a reduction in the rate of utilization of carbohydrate during the fast. The possibility that the evidence might also be interpreted as indicating increased glyconeogenesis from fat during the fast was indicated by Young (1937 B).

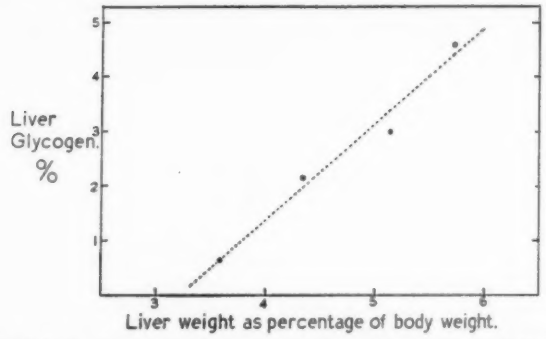

FIG. 5.—The data for the average liver glycogen percentage content, plotted against the average liver weight expressed as percentage of the body-weight, for groups of young rabbits receiving injections of different anterior lobe preparations, during a short fast (Marks and Young, 1938 B).

THE INFLUENCE OF ANTERIOR PITUITARY EXTRACTS ON KETOGENESIS.

In 1930 Burn and Ling showed that the administration of a crude anterior lobe extract to fat-fed rats resulted in a substantial increase in ketone excretion. The stimulating influence of the anterior pituitary gland on ketogenesis has subsequently been confirmed by a number of investigators, but as yet little is known of the nature of the active principle. The crude extracts used to produce diabetes in dogs in the experiments I have discussed above undoubtedly contain the pituitary ketogenic factor. An investigation of the nature and action of the ketogenic substance in these extracts is being undertaken by Dr. C. H. Gray (Gray, 1938).

The nature of the diabetogenic factor of anterior pituitary extracts.—Two years ago, after discussing the relevant evidence then available, I suggested (Young, 1936 A) that the diabetogenic action of anterior pituitary extracts in normal animals might be due to the combined actions of as many as three different factors. The evidence which has accumulated during the last two years has thrown no definite light on this question, but has shown quite clearly that a substance which is not diabetogenic in an intact dog can provoke a substantial glycosuria in a hypophysectomized-depancreatized dog (Long, 1937). Long has found that prolactin is particularly effective in this respect, and it seems probable that the glycotropic factor is the active principle concerned. As Long (1937) has pointed out, the evidence indicates that another factor, besides that inducing glycosuria in the "Houssay" (i.e. the hypophysectomized-depancreatized) dog, appears to be required for the production of glycosuria in the intact dog. Prolactin (glycotropic ?) preparations do not induce ketonuria in hypophysectomized-depancreatized dogs (Long, 1937) or in intact dogs or rabbits (Young, 1938 B) so that we must visualize the possibility that for the production of glycosuria + ketonuria (diabetes ?) in both the "Houssay" and the normal dog, the co-operation of the ketogenic pituitary substance is required. If, as seems possible, the labile factor essential for the production of glycosuria in the intact dog is less stable than the ketogenic factor of Burn and Ling (1930), then the assumption must be made that the co-operative action of at least three factors is necessary for the exhibition of diabetogenic activity in the intact dog, whereas only two may be required for the intensification of the diabetic condition of the "Houssay" dog. Further investigations are necessary, however, before any definite conclusion can be drawn concerning the identity of what may be called the diabetogenic complex of the anterior pituitary gland.

The difference in response of the "Houssay" dog and the intact dog to anterior lobe preparations is presumably due to the presence of the pancreas in the normal

animal. In this connexion it is interesting to note that Houssay (1937) finds that the pancreas of a dog made temporarily diabetic by daily anterior lobe injections, secretes less insulin than normal. The evidence for this belief rests on the results of experiments in which the pancreas of such a diabetic dog is grafted into the neck of a previously depancreatized dog. In such an experiment the blood-sugar of the depancreatized dog falls more slowly than when a pancreas from a normal dog is grafted. Any relationship between this observation and that of the " pancreotropic " action of anterior lobe extracts is not at all clear at present. The observations of Richardson and Young (1938) do not lead one to suspect that lesions of the pancreatic islets play a major role in the production of the temporary diabetes in injected dogs.

The mechanism of the diabetogenic action of anterior lobe extracts.—There are two classical theories concerning the cause of the glycosuria in diabetes: (*a*) That it results from an " overproduction " of sugar in the liver (Bernard, 1877); (*b*) that it is caused by a lack of utilization of sugar in the tissues which normally oxidize this material (Minkowski, 1893). The evidence for and against these two theories has recently been discussed at some length, from the point of view of their historical development (Young, 1937 c) and it is not necessary to discuss them generally at present. The evidence we have been considering concerning the action of anterior lobe extracts on carbohydrate metabolism in general (see Table II for summary)

TABLE II.—SUMMARY OF SOME BIOLOGICAL PROPERTIES OF ANTERIOR PITUITARY EXTRACTS.

Action	Crude saline extract	Glycotropic *	Diabetogenic †
(1) Diabetogenic action in normal dogs:—			
(*a*) Temporary...	+	0	+
(*b*) Permanent...	+	0	−
(2) Promotion of:—			
(*a*) Formation of islet tissue in pancreas ...	+	−	−
(*b*) Glycogen accumulation during a short fast	+	+	+
(*c*) Accumulation of liver fat	+	+	+
(*d*) Ketogenesis	+	−	−
(3) Inhibition of the action of insulin on:—			
(*a*) Blood-sugar level	+	+	+
(*b*) Muscle glycogen formation	+	+	−
(*c*) Peripheral utilization of glucose ...	−	+	−
(*d*) Liver glycogen level in young rabbits ...	0	+	+

+ = effective. 0 = ineffective. − = not tested.

* Prolactin preparation.
† Free from detectable prolactin, i.e. pigeon-crop gland stimulating substance.

provides support for the belief that an increased production and mobilization of carbohydrate, possibly from fat, may occur in the liver as the result of anterior lobe treatment, and that the peripheral utilization of sugar may be inhibited. Fat mobilization may also occur. Houssay and Biasotti (1931) believe that the anterior pituitary gland stimulates the production of sugar from protein, and although conclusive evidence is lacking, the possibility cannot be ignored that such production may occur at the expense of fat. The important observations established by Cori, Russell and Bennett, and their co-workers (see Russell, 1938, for a recent review) may also be interpreted as indicating that a diminished oxidation of carbohydrate occurs as the result of treatment with crude anterior pituitary extracts. It is possible, therefore, that in the normal animal the finely adjusted balance which is maintained between sugar production in the liver and sugar utilization in the extrahepatic tissues, is controlled by the balanced antagonistic actions of insulin and the anterior lobe diabetogenic factor, both acting peripherally on the muscles, as well as on the central production of sugar in the liver. As I have already suggested (Young, 1936 A) the case of the heart-beat may be analogous. The heart has the intrinsic property of beating rhythmically, although the actual rate and type of beat is adjusted by the mutually antagonistic actions of the sympathetic and parasympathetic nerve supplies. Similarly, inherent processes of manufacture of sugar in the liver and utilization in the peripheral tissues probably exist, these processes being intrinsic properties of the

relevant tissues; the precise mutual adjustment of the rates of these two processes is mediated by the endocrine system, the antagonistic actions of insulin and the pituitary factors playing an important role in this adjustment. If this is so, then freedom from diabetes is the result of a precise regulation of the relative potencies of the pancreatic and pituitary factors. If, for any reason, the regulation is faulty, so that pituitary effects predominate, then diabetes may result. The nature of the regulating mechanism is beyond our present discussion, but it should be mentioned that some workers believe that the hypothalamus is implicated.

The cause of the permanently diabetic condition resulting, in dogs, from anterior lobe treatment, does not become clear as the result of this discussion. Whether it is a secondary phenomenon, resulting from islet lesions produced by the temporary diabetes, or whether it is of primary significance, and induced by a mechanism independent of that causing the temporary phase of the diabetic condition, cannot be settled at present. The first possibility is perhaps the more probable, and if it is correct, then one may find clinically that a short period of diabetes mellitus due to overaction of the pituitary gland, may persist after the action of the hypophysis has returned to its normal level, the persistence being due to pancreatic islet lesions.

It is clear from the discussion that our knowledge of the role of the hypophysis in the ætiology of diabetes is still in a very elementary condition. The large number of published papers on this subject, often mutually contradictory, can be a source of embarrassment rather than an aid to future development. Perhaps few will disagree with the statement of that great physiologist, Claude Bernard, who is recorded as saying to a friend: "It is that of which we are aware which is a great hindrance to our learning that which is yet unknown to us."

REFERENCES

Anselmino, K. J., Herold, L., and Hoffmann, F. (1933), *Klin. Wchnschr.*, **12**, 1245.
Bernard, C. (1877), "Leçons sur le diabète et la glycogénèse animale", Paris.
Best, C. H., and Campbell, J. (1936), *J. Physiol.*, **86**, 190.
Best, C. H., Dale, H. H., Hoet, J. P., and Marks, H. P. (1926), *Proc. Roy. Soc.*, B., London, **100**, 55.
Burn, J. H., and Ling, H. W. (1930), *J. Physiol.*, **69**, 19P.
Collip, J. B. (1934), *J. Mt. Sinai Hosp.*, **1**, 28.
Cope, O., and Marks, H. P. (1934), *J. Physiol.* **83**, 157.
De Wesselow, O. L. V., and Griffiths, W. J. (1936), *Lancet* (i), 991.
Fisher, R. E., Russell, J. A., and Cori, C. F. (1936), *J. Biol. Chem.*, **115**, 627.
Goldblatt, M. (1929), *Biochem. J.* **23**, 243.
Gray, C. H. (1938), *Biochem. J.*, **32**, 743.
Himsworth, H. P., and Scott, D. B. McN. (1938 A), *J. Physiol.*, **91**, 447.
Id. (1938 B), *ibid*, **92**, 183.
Houssay, B. A., and Biasotti, A. (1931), *Endocrinology*, **15**, 511.
Houssay, B. A., and Magenta, M. A. (1925), *Compt. rend. Soc. de biol.*, **92**, 822.
Houssay, B. A. (1936), *New England J. Med.*, **214**, 961 and 971.
Id. (1937), *Am. J. M. Sc.* **193**, 581.
Long, C. N. H. (1937), *Medicine*, **16**, 215.
Marks, H. P. (1936), *J. Physiol.*, **87**, 15P.
Marks, H. P., and Young, F. G. (1938 A), *J. Physiol.*, **93**, 61.
Id., (1938 B), *ibid.*, **92**, 14P.
Minkowski, O. (1893), "Diabetes mellitus nach Pancreasextirpation", Leipzig.
Richardson, K. C., and Young, F. G. (1937), *J. Physiol.*, **91**, 352.
Id. (1938). *Lancet* (i), 1098.
Riddle, O., Dotti, L. B., and Smith, G. C., *Am. J. Physiol.*, **119**, 389.
Russell, J. A. (1938), *Physiol. Rev.*, **18**, 1.
Russell, J. A., and Bennett, L. L. (1936), *Proc. Soc. Exper. Biol. and Med.*, **34**, 406.
Young, F. G. (1936 A), *Lancet* (ii), 237 and 297.
Id. (1936 B), *J. Physiol.*, **87**, 13P.
Id. (1936 C), *Chem. Ind.*, **55**, 237.
Id. (1937 A), *ibid.*, **56**, 292.
Id. (1937 B), *J. Physiol.*, **90**, 20P.
Id. (1937 C), *Ann. Science*, **2**, 47.
Id. (1937 D), *Lancet* (ii), 372.
Id. (1938 A), *Biochem. J.*, **32**, 513
Id. (1938 B), *ibid.*, **32**, 524.
Id. (1938 C), *ibid.*, **32**, 656.
Id. (1938 D), *J Physiol.*, **92**, 15P.

Section of Otology

President—F. J. CLEMINSON, M.Chir.

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Observations on the Pathology of Ménière's Syndrome

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IT is the purpose of this paper to describe—as is believed, for the first time—the pathological changes in the temporal bones in two cases of Ménière's syndrome. In both death occurred shortly after operation for section of the 8th nerve. For the purposes of the present paper, the surgical factors concerned in the operative failure of these cases will be dealt with only in so far as they are related to the interpretation of the histological changes which are now to be described. Their detailed consideration will be reserved for a further publication.

INTRODUCTION

The close anatomical association of the sense organs of hearing and equilibrium within the internal ear has always supported the more general view that impairment of function of these organs, often paroxysmal in type, would be likely to result from a wide variety of pathogenic agents acting upon the sensory elements, the blood supply, or the labyrinth fluids. This general formula is accepted by Watkyn-Thomas [1], who states in a recent textbook that " we are justified in assuming that there is no one primary cause of Ménière's syndrome ".

In spite of the advantages of such a general outlook, the possibility must be welcomed of a closer differentiation by clinical methods of the pathological factors concerned in these cases: that is to say, by the establishment of the fact that in a significantly large group of cases, the signs and symptoms of acoustic and equilibrial disturbance present certain recognizable peculiarities in their mode of onset, in their type and degree, and in the course which they run over a period of years. This point of view has been ably put in two recent papers by Wright [2] and Crowe [3], who agree very closely both in their clinical identification of a frequently encountered

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type of case and in postulating therein the action upon the labyrinthine end-organs of a single type of pathogenic agent. Wright believes the condition to be due to bacterial intoxication of the labyrinth, and describes it as a focal labyrinthitis. Crowe is less specific in his view of the type of pathogenic agent, but ascribes the condition to a disorder of the normal conditions of pressure and chemical constitution of the endolymph. One further possibility is represented by the view of Dandy [4], who believes the site of the lesion to be in the trunk of the 8th nerve and not in the labyrinth.

Earlier reports upon the changes in the temporal bones in cases of so-called Ménière's syndrome are to our knowledge available in only two instances. In one of these, described by Witmaack [5], a neurofibroma was revealed in the basal coil of the cochlea. In the other, described by Videbech [6], a generalized encephalitis was discovered, apparently of traumatic origin. Within the cochlea there was found a degeneration of Corti's organ with collapse of Reissner's membrane.

The point of view which we ourselves are inclined to favour is the one supported by the papers of Wright and Crowe, namely that a considerable proportion of patients exhibiting this syndrome are recognizable upon clinical grounds as being the victims of a common type of labyrinthine disorder. Clinical observation, possibly over a period of years, alone justifies the exclusion from this group of cases of traumatic encephalitis and of acoustic neuroma, and for this reason the reports of Witmaack and Videbech are not considered relevant to the present paper. On the other hand, the clinical features of the present cases warrant their inclusion in the clinical group defined by Wright and Crowe, and the description of the anatomical changes in the temporal bones is, it is believed, the first of its kind to be recorded. The clinical history of the first case now follows.

Case I

Clinical history.—J. B., a dock labourer, aged 63, was referred to the Department of Neurosurgery at the London Hospital, by Mr. Maurice Sorsby, in December 1934, on account of attacks of vertigo. Apart from anthrax of the thumb when a young man, and occasional winter bronchitis, he had enjoyed good health until three years before admission, when he began to have mild attacks of vertigo, followed six months later by attacks of greater severity, at times associated with falling. Owing to attacks in the docks he was put off work for four months during 1932 and for five months in 1933; during each of these periods he was treated by Eustachian catheterization and sedative drugs, with slight relief. In 1934, five months before admission to hospital, owing to further attacks at work, he was discharged from his employment. His attacks became worse, and for two months before admission he did not venture into the street alone for fear of falling in the traffic.

The mild attacks began with a momentary sensation of hot flushing in the head, followed by a slight loss of balance. He could still walk during these attacks, with a tendency to go to the left in zigzag fashion, and with no certainty that when he put his foot down he would find a secure foothold, but after a dozen paces he would be all right again. In attacks of longer duration he would kneel to save himself from falling.

In the more severe attacks everything seemed to go black, and he had to sit or lie down. There was then no sensation of rotation or of movement of the ground, but instead a feeling that he was staggering about; this lasted for a half-hour and was followed by unusually prompt recovery. On three occasions he fell without warning, twice in a backward direction with momentary loss of consciousness; once he nearly fell out of a chair. After each of these attacks he was able to get up immediately and to walk steadily. On a few occasions he was awakened by an attack. There was no vomiting or diplopia with the attacks.

One year before the attacks began he noticed that he was becoming deaf in the left ear. This deafness was progressive, and always worse in the winter time. He had never had aural discharge, but much dry wax came from his ears, and during the times when this was profuse he noticed that he was deaf also in the right ear. From the time of onset of the deafness he was usually conscious of a drumming noise in the left ear; this varied in intensity with the deafness, but was not worse during the attacks.

Examination.—He was a well-built, rather plethoric type of man. Blood-pressure 138/92. Smell was slightly defective at both nostrils and there was fine nystagmus to the right, but neurological examination, apart from auditory and vestibular investigations, showed no abnormality. His gait was normal. *Examination of hearing:* Mr. Maurice Sorsby, to whom we are indebted for his records, had noted in the latter part of 1934 that both ear-drums were retracted, the left being worse than the right. The Eustachian tubes were patent. He noted also considerable loss of hearing, the lower tone limit being raised and the upper tone limit lowered. Bone conduction was shortened and Rinne's test positive. In the London Hospital it was found that he could hear whispers 2 ft. from the right ear and the ordinary speaking voice only 3 in. from the left ear. A cold caloric test, with the patient lying down, gave no response on the left side after three minutes' irrigation, on the right side nystagmus to the left after twenty seconds, but not vertigo.

Operation (December 18, 1934).—Under avertin and intratracheal gas-and-oxygen anæsthesia the left vestibular nerve and part of the left cochlear nerve were divided. The operation was unusually difficult because of the excessive thickness and hardness of all parts of the posterior fossa (2 cm. in thickness over the lateral sinus). In consequence of this the bony opening was smaller than usual. However, division of the nerve was effected without any untoward incident, except that throughout the operation and in spite of avertin, the blood-pressure was at an unusually high level. The highest level, 200/100, was recorded while the nerve was being divided.

Post-operative course.—He responded well after operation, but the same evening he became restless, and, during the night, unconscious, with rising pulse-rate and temperature, stertorous and bubbly breathing, small fixed pupils, absent corneal reflexes, flaccid limbs, diminished or absent tendon and plantar reflexes, and raised blood-pressure (170/90). The bladder became distended and the urine contained a trace of sugar and albumin. The wound was reopened twelve hours after the first operation, and there was tremendous tension and swelling of the presenting left lateral cerebellar lobe, associated with herniation of the tonsils through the foramen magnum, which could only be relieved by decompressing the foramen magnum and allowing fluid to escape from the cisterna magna. Part of the posterior surface of the left cerebellar lobe was also removed. There was no evidence of post-operative bleeding. After operation his condition improved, but he did not fully regain consciousness and his chest condition became steadily worse, with much purulent material in the trachea, and moist sounds and diminished breath-sounds all over the chest. This was treated by posture and intermittent tracheal suction, but the patient died on December 21.

Necropsy six hours after death showed an area of cavitation and hæmorrhage measuring $5{\cdot}8 \times 3{\cdot}0$ cm. in the white matter of the left cerebellar lobe and extending into the vermis and across the middle line. Both lungs showed congestion and œdema, and in the right lung there were a few nodules of bronchopneumonia.

Comment.—Various technical points in connexion with the operation of intracranial division of the 8th nerve will be considered in a later paper, but in passing it may be noted that this patient showed during the operation a tendency to arterial hypertension which may have contributed to the onset of cerebellar œdema and hæmorrhage, as did the smallness of the bony opening in the posterior fossa.

Pathological Report

The temporal bones were received at the Ferens Institute on April 22, 1936, in a 4% solution of formaldehyde in which they had been preserved since the post-mortem examination, which was carried out on December 22, 1934, six hours after death. They were fully decalcified in 1% nitric acid in distilled water under control by X-rays and were embedded in celloidin. Serial sections were made in the horizontal plane at 25μ. Every 10th section was stained with Ehrlich's hæmatoxylin and counterstained with a mixture of Biebrich scarlet and eosin.

Histological Findings

Right Temporal Bone

Pneumatization.—No air spaces are to be observed anterior to the cochlea. The area is occupied by cancellous bone, with delicate bony trabeculæ separating wide spaces containing fatty marrow. In the region surrounding the antrum the air spaces are poorly developed and their lining shows a moderate degree of chronic inflammatory change. There is thickening and fibrosis of the mucosa with scattered collections of leucocytes, chiefly small lymphocytes. In places the air cells contain masses of mucus and desquamated epithelium in varying stages of degeneration.

Labyrinth capsule.—This shows no abnormality. The fissula ante fenestram is present and well developed. No fissula post fenestram is present.

External auditory meatus.—Normal.

Tympanum.—The tympanic membrane is grossly thickened. At a point immediately anterior to the inferior extremity of the handle of the malleus its thickness was found by measurement to be 340 μ. The average thickness of the membrane measured in this way in six normal specimens was found to vary between 80 μ and 112 μ with an average value of 94 μ. Extensive chronic inflammatory changes are present in the tympanic mucosa ; the epithelium is generally preserved ; the submucosa is greatly increased in thickness and contains numerous inflammatory cells, chiefly small lymphocytes. Laidlaw's silver stain shows numerous fine collagen fibrils.

Vestibule.—The disposition and size of the endolymph spaces in the vestibule show no abnormality. The perilymph cistern in the region of the stapes footplate is of normal size. The state of development of the pneumatic and marrow spaces, the inflammatory changes in the tympanum, and the relations of endo- and perilymph spaces in the vestibule are depicted in fig. 1 (Plate I).

The Vestibular Sense Organs and the Semicircular Canals. Normal anatomy.—The macular epithelium of the utricle, saccule, and cristæ of the semicircular canals consists normally of a layer of cells of very even thickness, lying between a well-defined basement membrane and a superficial reticulated membrane through which project the hairs of the sensory cells. The sensory cells are relatively few and their nuclei are more or less centrally placed. The nuclei of the more numerous supporting cells lie scattered at all levels between the membranes and resemble the nuclei of the sensory cells in their size and structure, particularly under the conditions of fixation and staining which were employed in the present case. Under these conditions also the cytoplasm is poorly preserved and its shrinkage exposes the keratin filaments of the supporting cells. The nuclei however stain well with hæmatoxylin and show numerous well-differentiated chromatin granules.

(1) *The vestibular sense organs.*—The condition of the maculæ of the saccule and utricle in the present case is in close accordance with that described above as normal. There is no displacement of the otolith membranes and the density of the innervation is normal.

PLATE I.

FIG. 1 (Case I).—Right temporal bone. Low power view showing the chronic inflammatory changes in the tympanum. The cochlea and vestibule are normal.

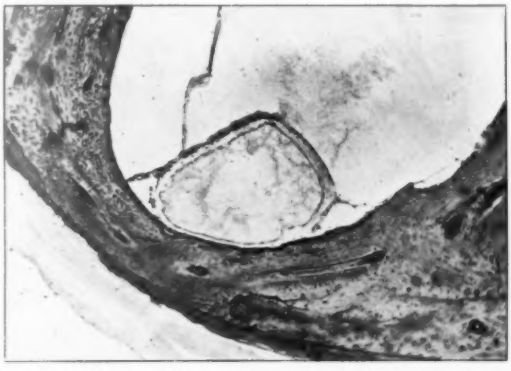

FIG. 2 (Case I).—Right temporal bone. Anterior vertical canal. The membranous canal contains a moderate amount of albuminoid coagulum. There is also a mild degree of subepithelial vesiculation. The changes are of doubtful pathological significance.

PLATE II

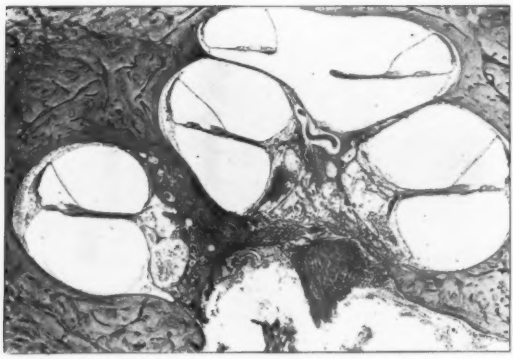

FIG. 3 (Case I).—Right temporal bone. The cochlea. No abnormality is present.

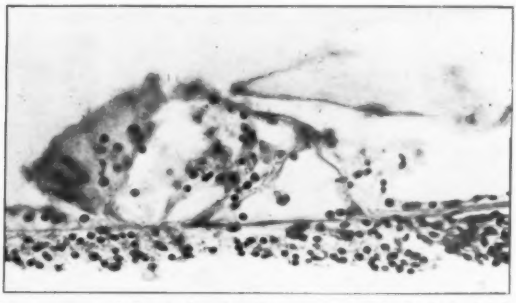

FIG. 4.—Human organ of Corti, showing the appearance typical of a fairly advanced degree of post-mortem degeneration.

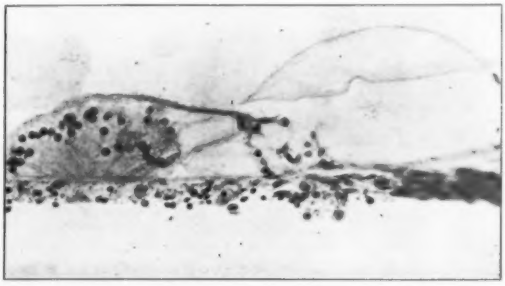

FIG. 5 (Case I).—Right temporal bone. Organ of Corti, showing a moderate degree of post-mortem degeneration. No pathological change is recognizable.

(2) *The semicircular canals.*—The epithelium and innervation of the cristæ show no abnormality. In the internal limb of the anterior vertical canal and in the lateral canal certain changes are present in the lining epithelium which are reproduced in fig. 2 (Plate I). The epithelium has been raised in localized excrescences apparently by the formation of subepithelial fluid collections. A similar condition of comparable degree is present in these areas in 7 out of 10 normal cases between the ages of 40 and 60 years. Its pathological significance must therefore be regarded as doubtful.

The cochlea.—This shows no abnormality, either in the disposition of Reissner's membrane or the density of the spiral ganglion. The stria vascularis is normal (fig. 3, Plate II).

Corti's organ.—The interpretation of anatomical changes in Corti's organ is notoriously difficult on account of the rapid progress of post-mortem disintegration, a difficulty which is particularly marked in the human subject. The histological features of this type of degeneration have been well established by the investigations of Eckert-Möbius [7] and others, and may be described briefly as follows :—

The cytoplasm shows a slight loss of density although the cell outlines are generally well preserved. The nuclei become pyknotic. More striking are the changes in form of Corti's organ as a whole, the cells of which show a marked tendency to break off and float away from the main mass. The tectorial membrane may undergo dissolution. Fig. 4 (Plate II) shows the condition typical of fairly advanced post-mortem degeneration of the human organ of Corti.

Fig. 5 (Plate II) shows the organ of Corti of the right temporal bone in the present case. It shows a moderate degree of post-mortem degeneration. No pathological change is recognizable.

8th nerve and internal auditory meatus.—The 8th nerve has been cut across at a point about 1 cm. central to the neuroglial-neurilemmal junction. The neuroglial portion of the nerve shows a very well-marked band of corpora amylacea, though these are not in excess of the amount normally present in this area at the age of the present subject. The nerve fibres and Scarpa's ganglion are normal. In the fundus of the meatus and between the diverging nerve bundles there is a considerable amount of structureless coagulum and inflammatory cells, chiefly polymorphonuclear leucocytes. This appears indicative of a moderate degree of meningeal reaction associated with the post-operative condition.

The aqueduct of the cochlea.—Scattered polymorphonuclear leucocytes are present throughout the length of the aqueduct, apparently derived from the subarachnoid space. Similar cells have been described in the fundus of the internal auditory meatus. In addition, there is a small collection of polymorphonuclear leucocytes adjoining the basilar membrane opposite the opening into the scala tympani of the cochlear aqueduct.

The saccus endolymphaticus.—The saccus and its surroundings display certain deviations from the condition defined as normal by Guild [8], and later by Anson and Nesselrod [9]. Fig. 6 (p. 60) is a diagrammatic representation of the mammalian ductus and saccus endolymphaticus according to Guild. The narrow tube lined by flattened epithelium is the ductus and all of the wider distal part is the saccus, which Guild divides into three parts, proximal, intermediate, and distal. The proximal and distal parts are lined by flattened epithelium and the intermediate part by a low columnar epithelium with recesses and papillary ingrowths. Surrounding this " pars intermedia " is a very loose vascular connective tissue.

In the course of another investigation Guild [10] was able to show by means of the Prussian-blue granule technique that the endolymph was absorbed through the wall of the pars intermedia into the loose perisaccular connective tissue.

A substantial confirmation of Guild's description has been provided by the examination of the temporal bones of 13 normal subjects between the ages of 30 and 60 years. In 11 of these there was a well-marked development of the perisaccular connective tissue as Guild describes. The condition is shown in fig. 7 (Plate III). Considerable deviation from this condition does however appear to lie within the limits of normal variation. In two of the temporal bones of normal subjects so examined the perisaccular connective tissue was very poorly developed, and in

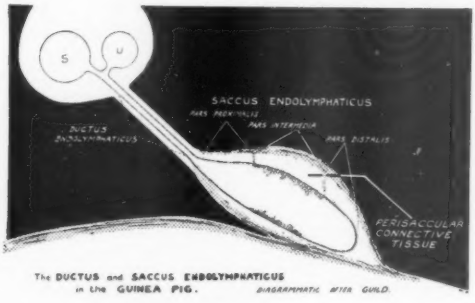

FIG. 6.

these the epithelium was brought into practically direct relationship with the dense material of the surrounding dura mater. This condition is shown in fig. 8 (Plate III).

The right saccus endolymphaticus of the present subject is shown in fig. 9 (Plate III). It is of interest in its close reproduction of the condition seen in fig. 8. That is to say, it belongs to the smaller anatomical group in which the " normal " area of perisaccular connective tissue is poorly developed.

Left Temporal Bone

Pneumatization.—There are no apical air spaces. The area anterior to the cochlea is occupied by wide-meshed cancellous bone containing fatty marrow. The air cells around the antrum are poorly developed and exhibit chronic inflammatory changes in their lining mucosa which are comparable in degree and extent to those described in the right temporal bone.

Labyrinth capsule.—This shows no abnormality. The fissula ante fenestram is present and well developed. No fissula post fenestram is present.

External auditory meatus.—Normal.

Tympanum.—Thickening of the tympanic membrane and chronic inflammatory changes in the tympanic mucosa are present and correspond closely in degree and distribution to those found in the right ear. The chronic inflammatory changes around the stapes footplates and round-window membranes in the two ears are shown in fig. 10 (Plate IV), which emphasizes their symmetrical distribution.

In addition there is a marked thickening of the posterior end of the stapes footplate. The thickening is maximal at the posterior extremity of the footplate and tapers rapidly towards the anterior extremity, which is of normal thickness. The adjacent annular ligament is not involved. The bone constituting the thickening shows a degree of hæmatoxylin retention usual in mature lamellar bone. It is composed of small irregular lamellar systems with a very few ill-marked cement lines. The marrow

PLATE III.

FIG. 7.—The human saccus endolymphaticus, showing the "normal" area of soft connective tissue surrounding the saccus.

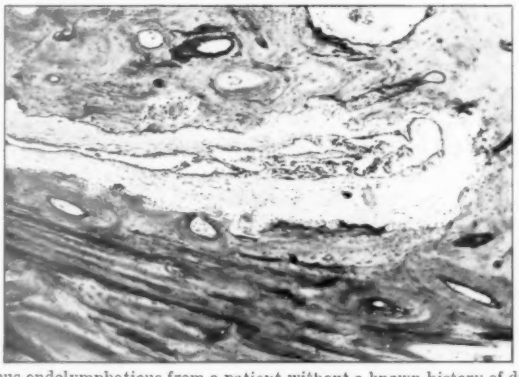

FIG. 8.—Saccus endolymphaticus from a patient without a known history of deafness. There is an atypical absence of the area of soft connective tissue around the saccus.

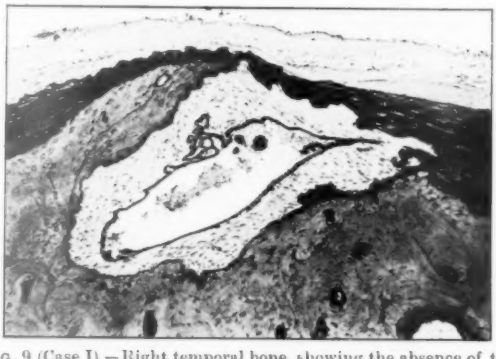

FIG. 9 (Case I).—Right temporal bone, showing the absence of the "normal" perisaccular connective tissue.

PLATE IV.

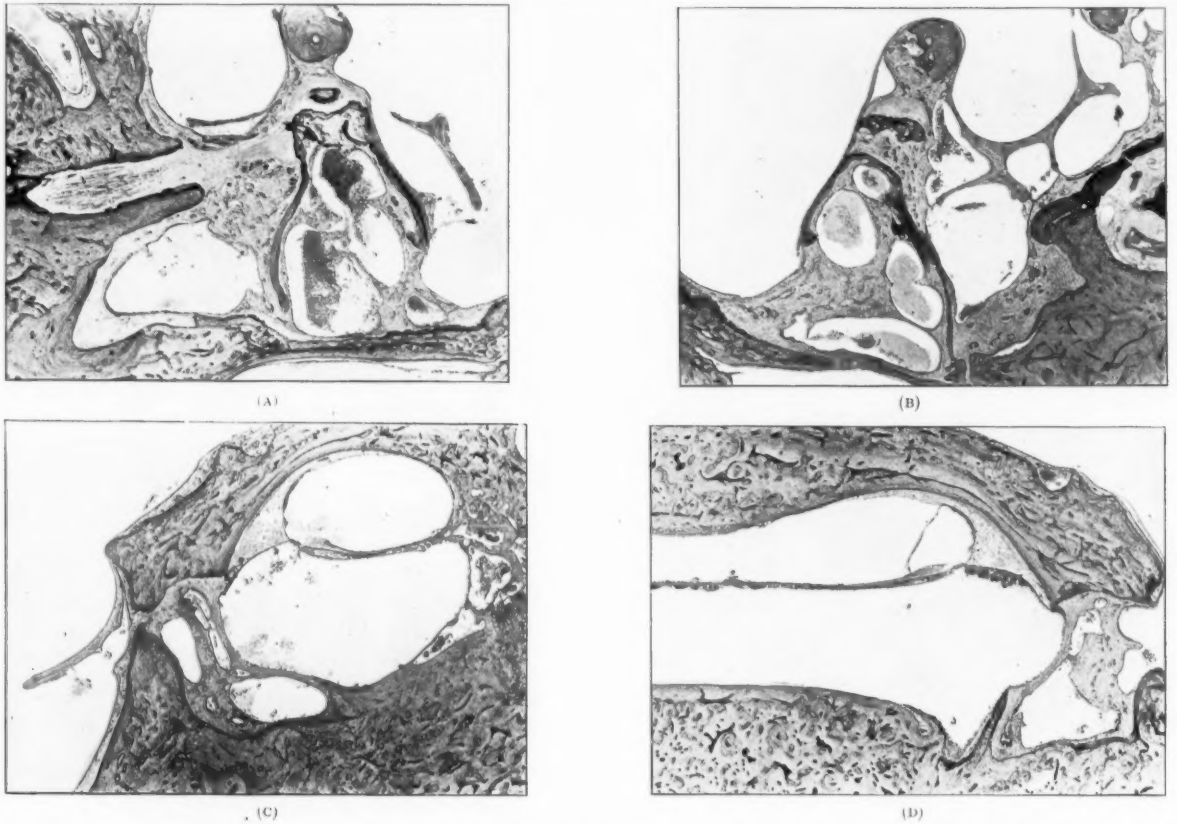

FIG. 10 (Case I).—A and C show the left stapes footplate and round window membrane. B and D show the same structures on the right side. Much chronic inflammatory granulation tissue is present in all four of the areas shown, with thickening of the round window membranes.

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FIG. 11 (Case I).—Left temporal bone. Low power view showing chronic inflammatory changes within the tympanum, and gross dilatation of the endolymph spaces of the vestibule and cochlea.

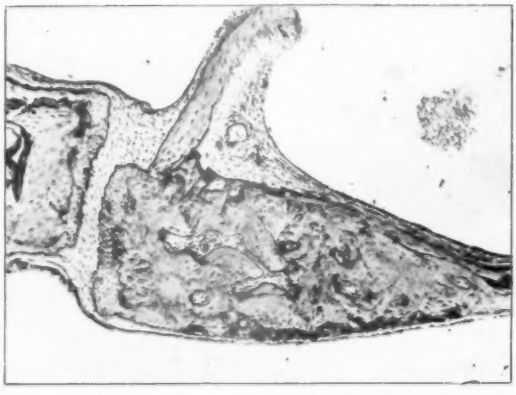


FIG. 12 (Case I).—Left temporal bone. Bony thickening, probably of inflammatory origin, of the posterior extremity of the stapes footplate.

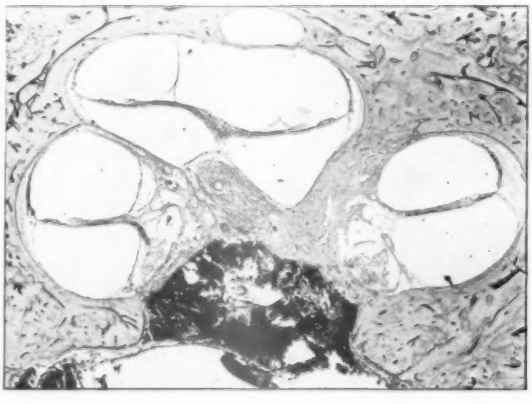


FIG. 13 (Case I).—Left temporal bone. The cochlea. Showing the maximal dilatation of the scala media. In the anterior basal whorl the displacement of Reissner's membrane is not complete. The membrane is fixed by newly formed connective tissue.

PLATE VI.

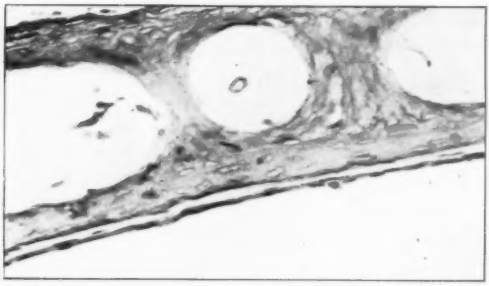


FIG. 14 (Case I).—Left temporal bone. Showing a view of the scala vestibuli. Reissner's membrane can be seen flattened against its bony wall.

FIG. 15 (Case I).—Left temporal bone. Fixation of Reissner's membrane (left) by organizing connective tissue elements.

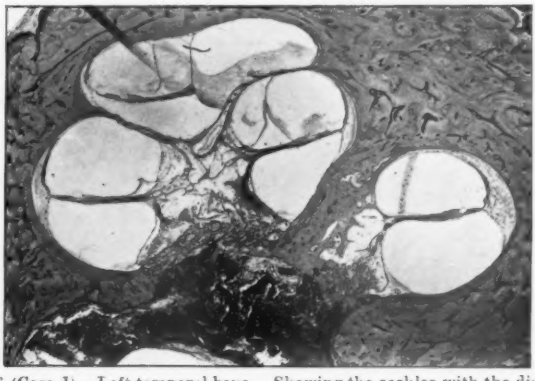


FIG. 16 (Case I).—Left temporal bone. Showing the cochlea with the displacement of Reissner's membrane through the helicotrema into the scala tympani.

spaces are moderately vascular, contain no inflammatory cells, and communicate in places by wide channels with the deep layers of the overlying mucosa.

The constitution of the bony mass favours its inflammatory origin without being incompatible with the view that it represents a late stage of otosclerosis. Localization of an otosclerotic lesion to the posterior extremity of the stapes footplate would however be unique, and this latter possibility must therefore be regarded as inadmissible.

The vestibule.—The disposition of the membranous walls of the utricle and saccule shows a marked abnormality. There is moderate dilatation of the utricle, particularly towards its upper part in the roof of the vestibule. At this point the small perilymph space lateral to the macula and on either side (anterior and posterior) of the point of entry of the utricular nerve has been obliterated. Lower, though still above the level of the oval window, this space persists although reduced in depth.

At the level of the stapes footplate the outstanding feature is an enormous dilatation of the saccule which occupies the whole of the vestibule with the exception of a small area occupied by the lower part of the utricle and the opening of the inner end of the lateral semicircular canal. The perilymph cistern which normally bounds the deep aspect of the stapes footplate has been obliterated. At a slightly lower level there can be seen a protrusion of the saccule into the perilymph space of the inner extremity of the lateral semicircular canal. In general, the greatly attenuated wall of the saccule can be traced in continuity. At the point described however a rupture of this wall into the perilymph space appears to have occurred. No interference can be demonstrated with the patency of the communicating pathways between the utricle, saccule, and ductus endolymphaticus, and the utricular fold (the possible valve-like action of which has been emphasized by Bast [11]) is seen in its normal position. The state of development of the pneumatic and marrow spaces, the inflammatory changes in the tympanum, and the dilatation of the saccular cavity are shown in fig. 11 (Plate V). Fig. 12 shows the changes in the stapes footplate at a higher magnification (Plate V).

The vestibular sense organs.—In both saccule and utricle the tissues deep to the macular epithelium are infiltrated with well-preserved red cells. These are continuous with the larger masses of red cells which occupy the fundus of the internal auditory meatus. The macular epithelium shows no abnormality apart from a moderate degree of post-mortem change. There is a slight degree of elevation of the otolith membrane from the utricular macula which is within the limits of artefact.

The semicircular canals.—No pathological changes can be recognized in the epithelium or innervation of the cristæ. The canal walls show a moderate degree of subepithelial vesiculation as described in the opposite ear. Its pathological significance appears doubtful.

The cochlea.—A low-power view of the cochlea is provided in fig. 13 (Plate V). At this magnification there is to be seen a striking abnormality in the disposition of Reissner's membrane. In places this seems to have disappeared. In fact, this appearance is brought about by a gross dilatation of the scala media with displacement of Reissner's membrane on to the wall of the scala vestibuli, with obliteration of its perilymph space. In places the displacement of the membrane is not complete, and here can be seen organizing connective tissue elements apparently anchoring the membrane in its new position.

Fig. 14 (Plate VI) shows a high-power view of Reissner's membrane flattened against the roof of the scala vestibuli. The typical double row of epithelial and endothelial nuclei described by Retzius can be distinguished. Fig. 15 (Plate VI) shows organizing connective tissue elements in the remaining niche of the scala

vestibuli, anchoring Reissner's membrane in its new position. Laidlaw's stain shows a number of small but thick collagen fibrils.

The dilatation of the scala media is particularly marked at the helicotrema, and Reissner's membrane has here been displaced through the helicotrema into the apical portion of the scala tympani. This condition is shown in fig. 16 (Plate VI).

The spiral ganglion is of normal density, and its cells show no pathological changes.

Corti's organ.—Pathological changes have occurred in Corti's organ in all the whorls of a mid-modiolar section. The tendency towards disintegration of the cell mass with detachment of its members typical of post-mortem degeneration is not marked. As judged by the relative positions of the cell nuclei, a considerable compression or shrinkage of the cell mass has occurred. In addition, a reddish-staining structureless coagulum is to be seen around the inner hair cells and filling Corti's tunnel. The staining reaction with hæmatoxylin shows a slight loss of differentiation on decolorization. As a result, Corti's organ appears rather more homogeneous than normal. The appearance found is shown in fig. 17 (Plate VII). It does not correspond to any fixation artefact obtainable with formaldehyde or to any known stage of post-mortem degeneration. It must therefore be regarded as definite evidence of some ante-mortem degeneration.

The stria vascularis.—Apart from a somewhat similar type of staining reaction with hæmatoxylin, the stria vascularis shows no recognizable abnormality.

The internal auditory meatus and 8th nerve.—The 8th nerve has been divided at the neuroglial-neurilemmal junction and has also been torn away at the fundus of the internal auditory meatus. It occupies the upper part of the meatus. The staining of the nerve fibres with hæmatoxylin is rather weak, especially at their central ends, where a good deal of disintegration of the myelin sheaths can be recognized. The cells of Scarpa's ganglion show no change apart from the presence of numerous deep red pigment-granules. The fundus of the internal auditory meatus contains a mass of red blood-cells which have infiltrated the subepithelial tissues of the maculæ of both saccule and utricle. A few polymorphonuclear leucocytes are to be seen fairly evenly distributed.

The aqueduct of the cochlea.—This is filled throughout its length with a pinkish coagulum containing red cells, endothelial cells, and a few polymorphonuclear leucocytes.

The saccus endolymphaticus.—As in the right temporal bone, there is to be seen a striking absence of the loose perisaccular connective tissue. The epithelium comes into relationship with a dense fibrous tissue inseparable from the surrounding dura mater.

Summary of the Pathological Changes found in the Temporal Bones (Case I)

(1) Chronic non-suppurative otitis media with thickening of the tympanic membranes in both temporal bones. Bony thickening of the posterior extremity of the left stapes footplate, apparently of inflammatory origin.

(2) Gross dilatation of the saccule and scala media in the left temporal bone with obliteration of the perilymph spaces of the vestibule and of the scala vestibuli.

(3) Degeneration of Corti's organ in the left temporal bone.

(4) Absence of the " normal " area of perisaccular connective tissue in both temporal bones.

Case II

Clinical history.—J. M., an engineer, aged 28, referred by Professor O'Donovan of Cork, was first seen in November 1936 on account of attacks of vertigo. Apart from

the fact that his mother was slightly deaf there was nothing relevant in his family or past history. His attacks of vertigo had begun four years before and, though frequent, had been quite mild until four months before admission, when he began to have violent attacks which caused him to give up his work.

The mild attacks occurred on an average about once a week, but were becoming more frequent. There was a feeling of eyestrain, then objects began to quiver, and finally to rotate. During these attacks he found that with practice he could continue to drive a car, but he had a peculiar sensation in the back of the head and a slight tendency to fall in whatever direction he shook his head. During the attack he was unable to read or to walk steadily. He vomited profusely with the first attack but not with others, though he was at times nauseated. The attacks usually passed off within ten minutes, though the first one lasted one and a half hours. Occasionally they wakened him from sleep.

The violent attacks occurred with little or no warning. Objects appeared to whirl rapidly, sometimes clockwise, but at other times anti-clockwise, and possibly also in other directions, though he was not sure of this. He usually collapsed to the floor. The violent rotation of objects lasted only a few seconds, but he would remain recumbent for from a half to one hour because objects still appeared to move, especially when he opened his eyes, and because of unsteadiness if he tried to walk. He could usually resume his work after one and a half hours. In these attacks he was quite unable to drive a car, and at times did not get enough warning to stop the car if the attack came on while he was driving. These violent attacks occurred on an average of about one a month. He never lost consciousness, or saw double in an attack.

As a child he had had earache, but he had never had aural discharge. In 1932, at the time of onset of the attacks, he had noticed that the hearing of his left ear was affected, and it gradually got worse, especially after the onset of the violent attacks in June 1936. With the deafness there was a continuous slight surging noise in his left ear which during the attacks became a ringing noise. A month before he was first seen he began to have ringing noises also in the right ear. Between the attacks he was perfectly well. From June 1936 he took luminal and bromides regularly, and his attacks became less frequent.

Examination.—He was a healthy-looking but rather nervous man, and the only abnormalities found were those connected with hearing and vestibular function. Blood-pressure, 134/70. Ocular movements were full, and there were nystagmoid jerks to the left. His ear-drums were normal. He heard a watch at 6 in. from the left ear and 4 ft. from the right. Air conduction was greater than bone conduction. Cold caloric tests produced nystagmus and moderate vertigo on each side after irrigation with cold water for one minute.

Comment.—As this patient had had considerable improvement with 1 gr. of luminal daily, even though he had not been able to return to work, it was decided to continue to treat him with larger doses of this drug, up to 3 gr. a day. With this treatment the attacks became much less frequent, and he was able to return to work, though not driving a car. But he felt "doped" with the luminal, and he continued to have both mild and violent attacks, one of them in front of a prospective employer. His work was a good deal with machinery. Accordingly, in April 1937 he returned for operative treatment. Lumbar puncture at this time showed a resting pressure of 145 mm. and normal cerebrospinal fluid. Before operation an audiometric examination was made (fig. 18), for which we are indebted to Dr. Phyllis Tookey Kerridge.

Operation (April 22, 1937).—The left vestibular nerve was divided in the cerebello-pontine angle and the operation presented no unusual difficulty. The posterior part of the foramen magnum was removed at this operation.

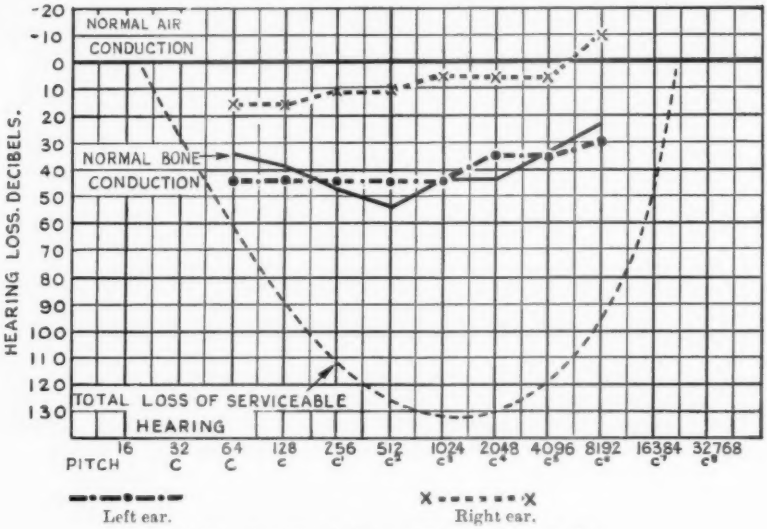


FIG. 18.—*Case II.* Audiogram showing air conduction.

Post-operative course.—During the first day after operation the course was satisfactory. There was the usual nystagmus, especially to the right, and tests with Bárány's box in the right ear showed good preservation of hearing in the left ear. During the second night the patient complained of slight headache and was restless, but gave no cause for alarm. On the following morning he suddenly became unconscious and died shortly afterwards while the operation wound was being reopened. This disclosed a moderate amount of blood-clot on the posterior aspect of the cerebellum and severe foraminal herniation of the cerebellar tonsils.

Necropsy, four hours after death, limited to the head, showed considerable congestion of the leptomeninges and a softened lacerated hæmorrhagic zone, measuring $3{\cdot}5 \times 3{\cdot}0 \times 4{\cdot}0$ cm., in the posterior aspect of the left lateral lobe of the cerebellum. The cisterns around the medulla oblongata were filled with blood-clot.

Pathological Report

The left temporal bone only was received at the Ferens Institute on May 24, 1937, in 4% solution of formaldehyde in which it had been preserved since the post-mortem examination, which was carried out on April 24, 1937, four hours after death. The dura mater had been stripped from the posterior aspect of the bone. No other macroscopic defect was to be observed. The bone was completely decalcified under control by X-rays in 1% nitric acid in distilled water. It was embedded in celloidin and serial sections were cut in the horizontal plane at a thickness of 25 μ. Every 10th section was stained with Ehrlich's hæmatoxylin and counterstained with a mixture of Biebrich scarlet and eosin.

Histological Findings

Pneumatization.—There is a well-marked development of the air-cell system around the antrum but not in the region anterior to the cochlea. The bone here is dense, with small intertrabecular spaces containing red marrow. The mucosa lining

PLATE VII.

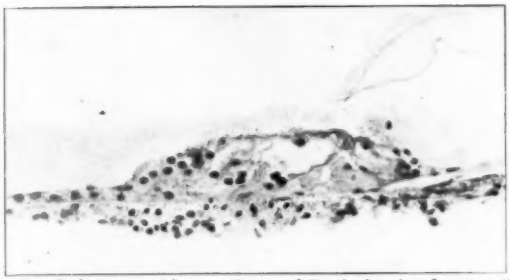


FIG. 17 (Case I).—Left temporal bone. Organ of Corti, showing degenerative changes.

FIG. 19 (Case II).—Low power view, showing normal condition of the tympanum. Within the labyrinth there is a gross dilatation of the endolymph spaces.

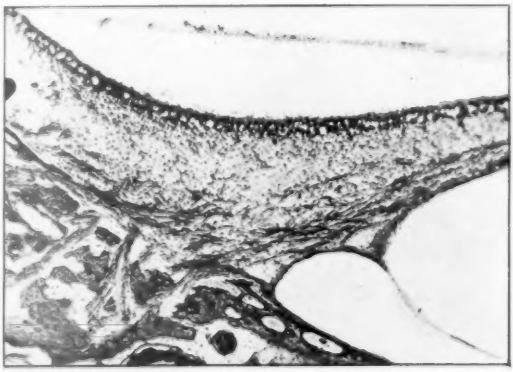
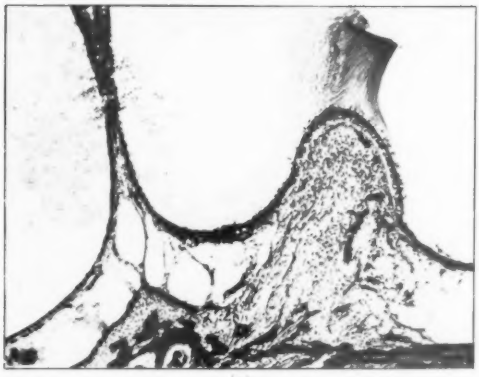


FIG. 20 (Case II).—Macula utriculi, showing a gross elevation of the otolith membrane with degeneration of the sensory epithelium.

PLATE VIII.



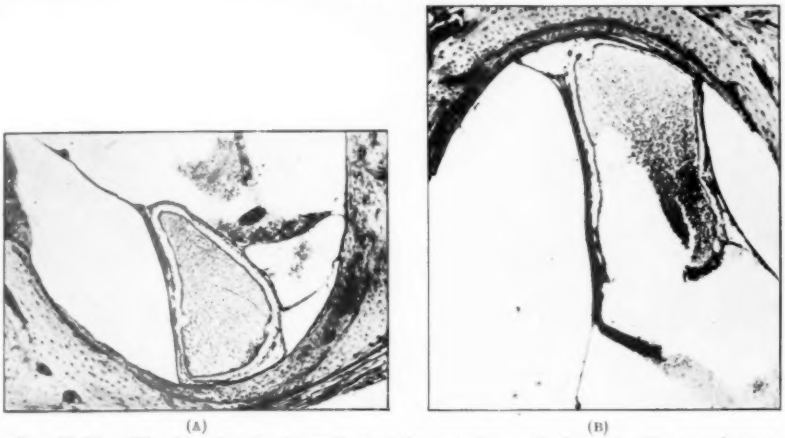
(A)

(B)

FIG. 21 (Case II).—Cristæ of the posterior (A) and lateral (B) semicircular canals, showing albuminoid coagulum upon the cupulæ and vascular engorgement, with degeneration of the sensory epithelium.

FIG. 22 (Case II).—Lateral semicircular canal, showing subepithelial vesiculation and albuminoid coagulum in the perilymph space.

PLATE IX.



(A) (B)

FIG. 23 (Case II).—Showing the inner limb of the anterior vertical canal. The membranous canal contains dense albuminoid coagulum. B shows a section at a level 75μ lower than that of A. Degeneration and rupture of the canal wall has occurred.

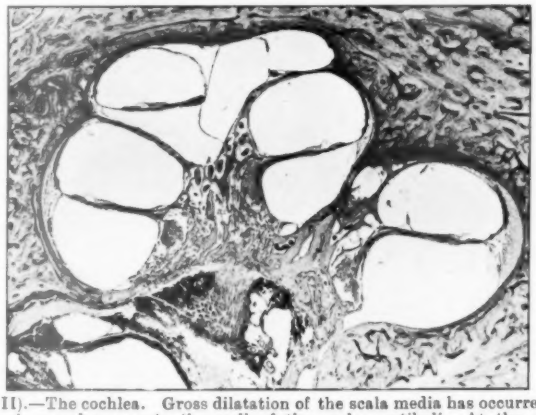


FIG. 24 (Case II).—The cochlea. Gross dilatation of the scala media has occurred with displacement of Reissner's membrane onto the wall of the scala vestibuli. At the apex Reissner's membrane has been displaced through the helicotrema into the scala tympani.

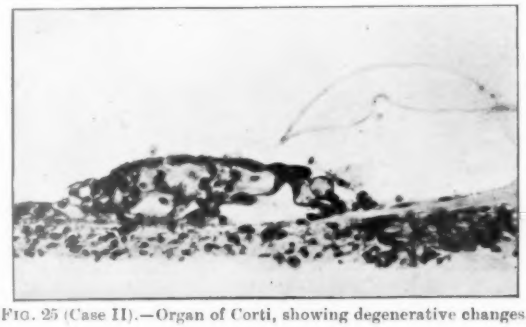
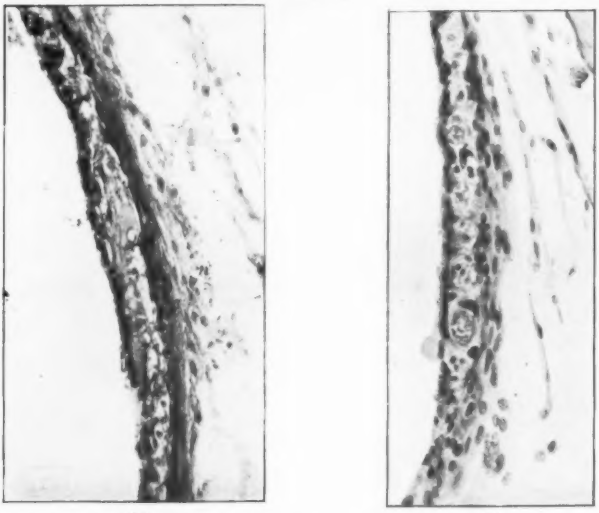


FIG. 25 (Case II).—Organ of Corti, showing degenerative changes.

PLATE X.



(A) (B)

FIG. 26 (Case II).—A shows the stria vascularis with gross degenerative changes. B shows the normal structure of the stria vascularis under comparable conditions of age, fixation, and staining.

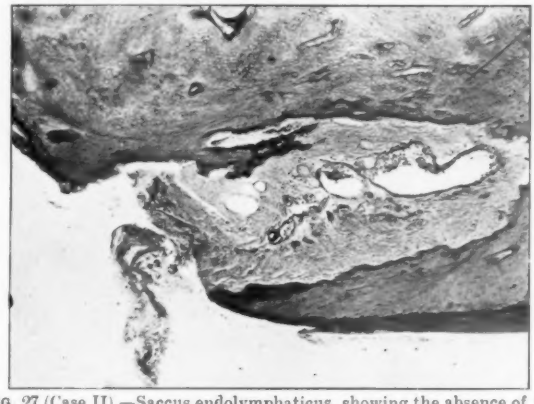


FIG. 27 (Case II).—Saccus endolymphaticus, showing the absence of the normal perisaccular connective tissue.

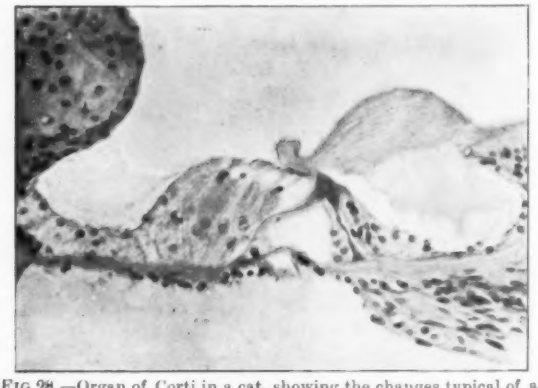


FIG 28.—Organ of Corti in a cat, showing the changes typical of a moderate degree of serous labyrinthitis.

the air cells is normal, apart from a slight degree of fibrosis in the submucosa and a conspicuous engorgement of the blood-vessels. This is also seen in the vessels of the marrow spaces.

Labyrinth capsule.—This shows no abnormality. The fissula ante fenestram is present and well developed. There is also a well-marked fissula post fenestram.

External auditory meatus.—Normal.

Tympanum.—The tympanic membrane and the middle-ear cavity are normal, apart from a marked engorgement of the vessels in the mucosa over the promontory and elsewhere.

The vestibule.—There is a gross dilatation of the endolymph spaces, in particular of the saccule. At the level of the stapes footplate the saccule extends around the lateral aspect of the utricle to enclose it on its posterior aspect and extends into the inner extremity of the lateral semicircular canal. The perilymph cistern has been obliterated.

The opening of the saccule into the ductus endolymphaticus contains a dense reddish-staining coagulum. The communications of the utricle and saccule with the ductus endolymphaticus are clearly observable and the utricular fold shows no displacement.

The condition of the pneumatic-cell system, the tympanum, and the endolymph spaces within the vestibule, is shown in fig. 19 (Plate VII).

The vestibular sense organs.—In both the saccule and the utricle elevation of the otolith membrane has occurred; this is of advanced degree in the utricle (fig. 20, Plate VII). The macular epithelium shows a well-marked abnormality in its staining reaction. Both cytoplasm and nuclei show an increased retention of the hæmatoxylin. Very little differentiation by acid is possible, either of the chromatin granules within the nuclei, or between the nuclei as a whole and the surrounding cytoplasm.

The semicircular canals.—The epithelium of the cristæ shows well-marked pathological changes of the type described in the case of the macular epithelium, though more marked in degree (fig. 21, Plate VIII). The epithelium is converted into a deeply stained ill-differentiated mass of nuclei cytoplasm, and keratin filaments. There is a marked engorgement of the vessels in the connective tissue framework. It should be noted however that a similar engorgement has been described in the vessels of the tympanic mucosa and of the bone-marrow. It is thus probable that this feature is part of a generalized terminal condition and is therefore without pathological significance.

The lateral canal shows a very marked formation of subepithelial vesicles (fig. 22, Plate VIII). The internal limb of the anterior vertical canal contains a very dense coagulum which retains the hæmatoxylin stain and gives a positive reaction to Gram's stain for fibrin (fig. 23 A, Plate IX). Fig. 23 B shows the same canal 75 μ lower. Here the canal wall has ruptured and has become converted, evidently by some degenerative process, into a strongly hæmatoxyphil fibrillated substance.

The cochlea.—Gross dilatation of the scala media has occurred, with displacement of Reissner's membrane on to the wall of the scala vestibuli. At the apex of the cochlea Reissner's membrane has become bulged through the helicotrema into the apical portion of the scala tympani. These changes are shown in fig. 24 (Plate IX).

Corti's organ.—A high-power view of Corti's organ is shown in fig. 25 (Plate IX). Corti's tunnel is well defined and crossing it can be seen a faint outline of the characteristic nerve filament. There is a marked abnormality of the staining reaction of Corti's organ throughout the cochlea. Differentiation of the hæmatoxylin stain is practically impossible: that is to say that selective retention of the stain by the nuclei and certain other elements after treatment with acid is abolished. Little nuclear structure can be made out, and the degree of hæmatoxylin retention as

a whole shows a marked increase. The result is a relatively homogeneous darkly-staining mass. The condition corresponds to no fixation artefact obtainable with formaldehyde or to any stage of post-mortem degeneration and is therefore regarded as definite indication of intravital degeneration.

The stria vascularis.—This shows conspicuous abnormalities in all whorls of the cochlea. The covering layer of flat epithelial cells is intact. As in Corti's organ, there is a marked increase of hæmatoxylin retention, with loss of differentiation both in the epithelium and in the deeper layers of the stria. In a few places the intercellular spaces in the deeper layers of the stria are filled with a structureless reddish-staining coagulum. This condition is shown in fig. 26 A (Plate X). Fig. 26 B shows the structure and staining reaction of the stria which is found in normal human material, fixed and stained in a comparable manner.

The internal auditory meatus and 8th nerve.—The 8th nerve has been divided through its neurilemmal portion. The staining reaction of its fibres with hæmatoxylin shows no abnormality except in the region which adjoins the point of section. The staining here is very weak and a good deal of disintegration of the myelin sheaths can be made out.

The cells of Scarpa's ganglion appear to be of normal number. In about 50% of these cells early degenerative changes have occurred. The cell outlines have faded. The granules in the cytoplasm which in the normal human subject show so striking an affinity for the Biebrich scarlet counterstain, are either absent or much reduced in size and number. The nuclei are pyknotic with a very conspicuous crenation of their edges.

Large masses of red cells occupy the spaces around the nerve-trunk and between its constituent bundles. These masses are particularly dense at the fundus of the meatus. A few polymorphonuclear cells are present and are evenly distributed throughout the area.

The aqueduct of the cochlea.—This is occupied throughout its length by dense masses of red cells with a few scattered small lymphocytes and polymorphonuclear leucocytes. None of these cells is to be seen in the scala tympani adjoining the opening of the aqueduct. The perilymph space here contains a large amount of dense albuminoid coagulum.

The ductus and saccus endolymphaticus.—The ductus is patent and shows no abnormality. The pars distalis of the saccus has been distorted by the removal of the overlying dura mater. Its lumen contains some epithelial debris and a few red cells. The most noteworthy feature is the absence of the "normal" area of loose connective tissue between the saccus wall and the surrounding area. A few red cells can be seen in the meshes of the fibrous tissue deep to the epithelium. Evidence of an inflammatory process is however absent. The condition of the saccus is shown in fig. 27 (Plate X).

Summary of the Pathological Changes found in the Left Temporal Bone (Case II)

(1) Gross dilatation of the saccule and scala media with obliteration of the perilymph cistern and of the scala vestibuli.

(2) Degeneration and rupture of the wall of the anterior vertical membranous canal, associated with the presence within its lumen of dense albuminoid coagulum.

(3) Degeneration of Corti's organ.

(4) Degeneration of the epithelium of the maculæ and of the cristæ of the semicircular canals.

(5) Degeneration of the stria vascularis.

(6) Absence of the "normal" area of perisaccular connective tissue around the saccus endolymphaticus.

Discussion

The data now at our disposal invite inquiry from two points of view. There is required in the first place a reconstruction of the natural history of the morbid anatomical changes which have been described, and in the second place an explanation in terms of these changes of the clinical features of the disease.

(1) *The Development of the Pathological Changes*

The pathological changes in the affected temporal bones of the two cases may be summarized as follows :—

There is a gross dilatation of the endolymph system which affects chiefly the scala media of the cochlea and the saccule. Degenerative changes are present in Corti's organ in both cases, and in the stria vascularis in the second case only. Scattered albuminoid coagula are present throughout the endolymph spaces. This coagulum is particularly dense in the anterior vertical canal of the second case, and at one point degeneration and rupture of the canal wall has occurred.

In very general terms such changes correspond to those described by Witmaack [12] as representing the reaction of the labyrinth to damage from bacterial or other toxins reaching it through the round window or via the blood-stream. To this reaction, commonly known as serous labyrinthitis, he has given the name of " hydrops labyrinthi " ; and in the present instance it would be justifiable to describe the tissue changes as representing such a serous labyrinthitis, in the first case in response to toxins passing through the round-window membrane, and in the second case to toxins reaching the internal ear via the blood-stream from some unspecified focus of infection, in accordance with the view of Wright [2].

While no decisive objection can be made to this interpretation, it is necessary to emphasize that such extreme and uniform dilatation of the endolymph system is extremely rare in serous labyrinthitis, and secondly that while the histological changes in Corti's organ revealed in the present cases may represent some undescribed stage of serous labyrinthitis, they do not present those features which are described by Witmaack and others as being most typical of this condition, a characteristic example of which appears in fig. 28 (Plate X). This shows the organ of Corti in a cat, with the changes typical of a moderate grade of serous labyrinthitis. The hair cells have mostly disappeared. There is a fading of the intercellular boundaries and the cell protoplasm presents a stippled appearance, possibly due to small fluid-containing vacuoles.

It must further be considered that some at least of the tissue changes must be regarded as representing a reaction of the labyrinth to the operative interference and the resulting meningeal reaction. In particular should be mentioned the albuminoid coagulum in the scala tympani adjoining the opening of the cochlear aqueduct as well as the collections of leucocytes in this region and in the lumen of the duct itself. It is however unlikely that such an explanation can be extended to other of the changes, notably the dilatation of the endolymph system. This view has been controlled by an examination of the temporal bones in five cases of 8th-nerve tumour in which death occurred a few days after operative removal. (The histological preparations and clinical histories of two of these cases were kindly placed at our disposal by Mr. Philip Scott, to whom our thanks are due.) In all of these, considerable collections of red cells were found in the fundus of the internal auditory meatus with scattered polymorphonuclear leucocytes. In all there was a well-marked serous labyrinthitis with albuminoid coagulum in the perilymph spaces. This was less

marked in the endolymph spaces, and nowhere so dense as that described in the second of the present two cases in association with rupture of the wall of the anterior vertical canal. In all the cases Corti's organ and the stria vascularis showed no change apart from post-mortem degeneration. In two of the cases some dilatation of the endolymph system was present, confined to the scala media of the cochlea and characterized by a relatively insignificant displacement of Reissner's membrane. The much greater degree and extent of the dilatation of the endolymph system in the present cases, associated, as it was in places, with fixation of Reissner's membrane by organized tissue elements, appear to exclude the possibility of the changes being the result of an acute reaction to operative interference.

The available evidence must therefore be regarded as opposing the view that the tissue changes described are attributable to a reaction of the labyrinth, either to operative interference or to an affection of longer standing by bacteria or their toxins, and additional emphasis must accordingly be thrown upon the condition found in and around the saccus endolymphaticus in all of the three temporal bones which have been examined. It will be recalled that in all of these the soft perisaccular connective tissue, identified by Guild as the normal absorption area of the endolymph, was found to be absent. It might well be that the general dilatation of the endolymph system in these cases was due to hypersecretion and had led to the obliteration by pressure of the soft perisaccular tissue. But this seems to be rendered unlikely by the fact that in the unaffected ear of the first case the same absence of this perisaccular tissue is to be seen. The suggestion is therefore made that the endolymphatic dilatation in these cases is due, at any rate in part, to some failure in the normal absorptive mechanism, and that morphological evidence of this failure is provided by the absence from these cases of the normal absorption area of perisaccular connective tissue.

It should however be clearly emphasized that a similar absence of this connective tissue was found in two of the 13 normal cases examined, and that it is impossible upon the basis of this material alone to regard this anatomical condition as more than a normal variation which acts as a predisposing factor in bringing about the dilatation of the endolymph system.

The primary change may still be either an increased production of the endolymph itself, or else some more inscrutable type of alteration in its physico-chemical constitution as suggested by Crowe. It is clear for instance that a continued secretion of endolymph of an abnormally high ionic concentration might well lead to such a dilatation of the endolymph system by osmotic attraction of water molecules through its membranous walls from the surrounding perilymph. One feature of the endolymphatic dilatation remains to be considered in greater detail, namely the relative immunity of the utricle to the process of dilatation which is so strikingly completed in the case of the saccule. Obstruction to the entry of the endolymph is excluded as an explanation by the finding of normal conditions of communication between the utricle and the ductus endolymphaticus. An alternative explanation might obviously be sought in a relatively greater rigidity of the utricular wall.

Although Retzius [13] gives a very full description of the form and position of the human utricle and saccule, no details are provided concerning the relative thickness of their walls. Further evidence upon this question has been provided by a study of three transparencies of the human labyrinth which were prepared and kindly placed at our disposal by Mr. E. W. Peet. Stereoscopic examination of these specimens with a low-power dissecting microscope under a dark-ground illumination shows considerable differences in the apparent thickness of the walls of the utricle and saccule. The utricular wall, particularly in its upper part, possesses a conspicuously greater density.

Examination of normal temporal bones confirm this impression. Three series of horizontal sections cut at 25 μ thickness were examined. Considerable possibility of artefact may obviously be brought about by the obliquity in sections of this thickness of the membranes in question, but this would appear to be excluded by the finding that the average thickness of the utricular walls was about two or three times greater than that of the saccular walls. This conclusion was arrived at by assessing by eye the average difference of the thickness of the utricular and saccular walls in each of the sections in turn. In 70% of the sections the ratio in favour of the utricular wall varied between two and three to one. In the remaining 30%, the utricular and saccular walls were of comparable thickness. These results may therefore be taken as providing a satisfactory explanation of the relatively greater dilatation of the saccule in the affected labyrinths in the two cases under present discussion.

(2) *The Relationship of the Pathological Changes to the Clinical Condition*

From the purely clinical point of view the most interesting speculation must be to explain in terms of the anatomical changes the most salient feature of the disease, namely paroxysmal disorder of labyrinthine function.

Fig. 29 A, p. 70, shows a diagram of the normal labyrinth. The membranous labyrinth is a closed fluid system, and the mechanism for the secretion and absorption of the fluid is resident within its walls. Surrounding it is the perilymph, which reaches the perilymph spaces via the aqueduct of the cochlea from the relatively enormous cisterns of the cerebrospinal subarachnoid space. In this fluid system it is clear that any volume increase in the endolymph will be met by an expansion of its thin and elastic membranes, and by the expulsion through the helicotrema and cochlear aqueduct of a corresponding volume of perilymph. The resulting pressure change in the fluid system as a whole will be equivalent to that following the injection of a fraction of a c.c. of fluid into the spinal theca, that is to say, negligible.

A simplified representation of such a fluid system is provided by the smaller diagram of a rigid-walled narrow-necked vessel containing fluid. Within it is an elastic-walled balloon containing a separate fluid. A volume increase of the fluid within the balloon could clearly only lead to the ejection along the bottle-neck of a corresponding amount of the surrounding fluid, with little change of pressure in the system. If however the endolymph system becomes fully dilated, then a very different state of affairs is brought about. The elastic membranes are everywhere brought into contact with the rigid bony walls, except at the helicotrema. At this point Reissner's membrane is stretched and bulges into the scala tympani and in this relatively limited space represents the sole area of elastic expansion which now remains. This condition is represented by fig. 29 B. Here the balloon has become expanded to fill the bottle and the last remaining area for elastic expansion is the relatively limited area in the bottle-neck itself. It is easy to see from this that the pressure change resulting from any sudden volume increase of the fluid within the balloon would be very considerable, and would in fact be reproduced approximately by the injection into an already filled rigid vessel of an infinitesimal quantity of fluid. In other words, once the dilatation of the endolymph system has attained its maximal degree, then the fluid system of the membranous labyrinth, from being insensitive, becomes at once extremely sensitive in its pressure response to a given volume increase of the endolymph.

In this way it seems possible to explain the attacks as being due to rapidly initiated bouts of asphyxia of the labyrinthine end-organs, brought about by extremely rapid rises of fluid pressure, in response to relatively very small volume increases in the endolymph. Upon the basis of this hypothesis it is supposed that there exists a

chronic condition of lowered function of the affected labyrinth due to increased endolymph pressure and resultant anoxæmia of its end-organs. This condition fluctuates in a manner typical of the clinical course of the disease, and may proceed during the course of the attack to complete paralysis of the affected labyrinth. In the chronic state between the attacks, and particularly during the days preceding an attack, there may exist a state of chronic unsteadiness which is much aggravated by sudden movements of the head. In accordance with the well-established principle that vertigo in unilateral labyrinthine disease nearly always originates from excitation of the more active labyrinth, this condition would be explained by stating that such head movements evoke a greater response from the sound labyrinth and bring about vertigo by the relative absence of a corresponding response from the affected labyrinth.

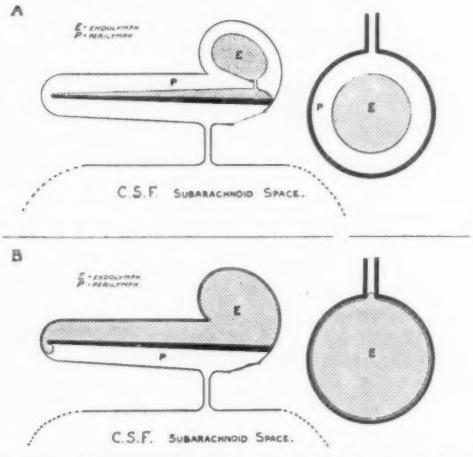


Fig. 29.—Diagrammatic representation of the fluid system within the labyrinth. A, Normal. B, With maximal dilatation of the endolymph system.

In such a patient it might well be that the caloric reaction would be grossly defective in the affected ear.

Relief from this condition might clearly be obtained by progress of the disease to complete death of the labyrinth, followed by the usual process of central compensation. This however occurs relatively seldom, and the condition which is typically encountered might be described as a chronic relapsing state of lowered function of the affected labyrinth. Similar relief might alternatively be obtained by surgical exenteration of the labyrinth or by section of the 8th nerve.

It should be noted that Crowe [3] adopts a different view of the functional state of the affected labyrinth which he considers to be strongly excited in the course of the typical attacks. It may obviously be objected to this view that such cases may show marked deficiency or even absence of the caloric reaction. This objection Crowe meets by suggesting that the stimulus which is responsible for the attacks is even stronger than that involved in the caloric reaction, a suggestion which is however difficult to accept in the absence of any information regarding the nature of the supposed stimulus.

Crowe further explains the sensitivity of these patients to rotation by stating that their reaction to this test, and not to the caloric test, is due to the stronger stimulus provided by the former. It would, we consider, appear unjustifiable to describe the stimulus provided by a relatively long-continued endolymph movement, such as occurs in the caloric reaction, as being physiologically weaker than the more natural stimulus provided by rotation, or indeed to attempt any such comparison. The view should in our opinion be preferred that in the rotation test equal stimuli are applied simultaneously to both labyrinths and so expose a condition of imbalance due to lowered function upon the affected side. These patients are more sensitive to this test than to the caloric test, since in the latter the stimulus is applied to one labyrinth at a time and involves no such exposure of their imbalance.

If, finally, for the sake of argument, it were to be assumed that increased endolymph pressure is the stimulating factor postulated by Crowe, it is difficult to understand how this could act upon the end-organs of the semicircular canals, since the cupular displacements which are required for their excitation could not be brought about by a simple and evenly distributed increase of endolymph pressure.

For these reasons it is considered that Crowe's hypothesis has less in its favour than that which has now been put forward, namely, that the symptoms of labyrinthine disorder are due to a lowered functional state of the affected labyrinth due to anoxæmia of its end-organs, induced by a raised pressure of its endolymph.

This explanation of the mechanism of the characteristic attacks involves certain assumptions. In the first place it must be believed that the secretory pressure of the endolymph may attain a level which would materially curtail the vascular supply of the labyrinthine end-organs. This belief would be compatible with the high-pressure levels which are known to be attainable by other secretions, notably the saliva.

In the second place it is necessary to suppose that a certain pressure level which is sufficient to bring about an anoxæmia of the labyrinthine end-organs, and so to precipitate an attack, is nevertheless insufficient to interfere, at any rate for short periods, with the secretory activity of the stria vascularis itself which is primarily responsible for inducing and sustaining this pressure level. This supposition might be taken as representing a difference in sensitivity to a given degree of anoxæmia between the stria vascularis and the labyrinthine end-organs, but an alternative explanation appears to be provided by certain morphological differences in the vascular supply of these structures.

The maculæ and cristæ are supported by a soft connective tissue framework with a fairly rich capillary network which is closely related to the overlying epithelium [14]. A different condition is found in the stria vascularis, the deeper layers of which are notable for the presence of numerous small arterioles. More recently, the course and structure of these arterioles have been studied in greater detail by Belemer [15]. The vessels pass from the modiolus across the roof of the scala vestibuli and enter the stria at its upper border. Thereafter they pursue a course of varying obliquity through the stria, to emerge once more from its lower border into the substance of the spiral ligament.

Belemer duly emphasizes the remarkable character of an anatomical arrangement whereby arterioles entering a capillary field so small and well defined as the stria vascularis, should also leave it with their form substantially unchanged. He makes the suggestion that the arterioles, by variation in their calibre, may influence the tension of the basilar membrane, and supports this suggestion with his observation of a particular relationship of the emerging arterioles to the oblique fibres of the spiral ligament. With this suggestion we are less concerned than with the demonstrated

existence of numerous arterioles within the stria, the maintenance of their calibre in their passage through the stria, and finally their necessarily intimate relationship to its secretory elements.

These facts appear to necessitate the belief that the capillary supply from the arterioles to the secretory elements is delivered at a particularly short range and consequently at a particularly high pressure, an arrangement which would clearly confer upon the stria vascularis a peculiar competence to maintain its secretory function under conditions of increased pressure in the surrounding fluids.

Upon this basis it would be possible to explain the difference, during a typical attack of vertigo, between the functional impairment of the vestibular end-organs and of the secretory elements of the stria vascularis as being due, not as first suggested, to a difference in sensitivity to the same degree of anoxæmia induced by a given rise of endolymph pressure, but to a difference in the degrees of anoxæmia so produced in these two sets of structures. This difference would be settled in favour of the stria vascularis by those peculiarities in its vascular supply to which attention has been drawn.

In connexion with the impairment of cochlear function which constitutes one of the clinical features of the disease, certain questions arise which can at present be dealt with only in a comparatively speculative manner. This impairment of function might clearly be explained in terms of increased endolymph pressure by postulating either an anoxæmia of the sensory elements or some mechanical interference, either with the structure of the sensory cells, or with the vibrating system as a whole. It may be recalled, with regard to the first possibility, that Kolmer [16] and others have already pointed out the absence of demonstrable capillaries in the organ of Corti itself and have indicated the quite logical conclusion that the tissue respiration of Corti's organ may be conducted through the medium of the endolymph. Crowe [3] has recently emphasized this important possibility. Upon this basis it may be supposed that increased endolymph pressure, at least in its earlier stages, would not alone lead to anoxæmia of Corti's organ in view of the maintenance of the partial pressure of oxygen which would result, and it would therefore be necessary to suppose that there occurs some additional change in the quality of the endolymph.

Explanation upon a mechanical basis of the impairment of hearing brought about by increased endolymph pressure is even more confined to speculation. It is clearly permissible to envisage some degree of structural disintegration by pressure of the sensory elements of Corti's organ, though its exact nature and extent cannot well be estimated.

Alternatively, there may result an increased impedance in the vibratory mechanism as a whole. The moving parts of the cochlea which are principally involved in hearing are the basilar membrane and the structures which occupy the round and oval windows. In the present instance, the round-window membrane would be unaffected by the dilatation of the endolymph system and may therefore be omitted from the argument. The other two structures are exposed to the increase of pressure and would be correspondingly stretched. Whether or not such stretching would be attended by an increased mechanical impedance would depend upon the elastic qualities of the structures in question. In elastic bodies of a certain quality equal increments of tension may lead to equal increments in length over a wide range; and if this were true in the case of the basilar membrane and annular ligament of the oval window within the possible range of endolymph pressure, then stretching of these structures within these limits would not be attended by any increase in their mechanical impedance. It would not in these circumstances be necessary to anticipate that endolymph hypertension would of necessity bring about a conduction type of deafness.

It might well be expected however that a generalized stretching of the basilar membrane would lead to a change in the natural frequency of its components, and it follows that suitably designed clinical observation of patients in the less acute stages of a typical attack might lead to information of importance regarding the resonance hypothesis. That is to say, by the recognition in these cases of a systematized type of "paracusis dysharmonica".

With regard to tinnitus, it cannot be said that the anatomical changes found in the present cases provide any new evidence which bears either upon its mode of origin or upon the well-known but puzzling fact that following section of the entire 8th nerve cessation of the tinnitus occurs in only a proportion of cases, although relief from the vestibular symptoms is the almost invariable rule. It is true that excitation of the cochlear end-organs might be expected to result from the degenerative changes which have been described in Corti's organ. This explanation cannot however be accepted without question. In end-organs of this type which are designed to respond to rapid and intermittent stimulation the process of adaptation is extremely rapid. It might thus be argued that a degenerative process of the type described would bring about a more constant type of stimulation, and one which on this account would be particularly incompetent to excite the rapidly adapting receptors of Corti's organ.

With regard to the persistence of the tinnitus after section of the 8th nerve which is known to occur in a considerable proportion of cases, it is only possible to attribute this to the development of certain obscure changes in the central cochlear neurones, similar in nature to those which may be responsible for painful phantom limb and other sensations of central origin.

It is of interest finally to note that under the abnormal conditions of fluid pressure which are indicated by the anatomical findings in the present two cases, there would necessarily occur a marked increase in the sensitivity of the internal ear to displacements of the stapes footplate resulting either from Eustachian obstruction or impaction of wax upon the tympanic membrane. Under normal conditions such displacements would lead to the expulsion of corresponding amounts of perilymph through the aqueduct of the cochlea with negligible rises of pressure in the fluid system as a whole. In the presence of a maximal dilatation of the endolymph system, such an escape of perilymph would be impossible, and a considerable rise of pressure in the endolymph system would thus occur. It is equally clear that this situation would be open to dramatic alteration by removal of the wax or by Eustachian inflation.

Although such clinical experiences compel the recognition that these and other tympanic abnormalities may precipitate the paroxysms so characteristic of the disease, the possibility clearly exists that they might further be interpreted as indicating the existence of some primary condition within the labyrinth which has rendered it vulnerable to such abnormalities; and that finally, the nature and mechanism of this primary condition may be related to that which has now been described.

Summary

Attention is drawn to recent publications by Wright and Crowe on the clinical aspects of Ménière's syndrome. In these, the opinion is expressed that a considerable proportion of patients exhibiting this syndrome are the victims of a common type of disorder of the internal ear.

Evidence in support of this view is provided by the present paper, in which are described the histological changes in the temporal bones of two such patients. In each of these the affected temporal bone showed a gross distension of the endolymph

system together with degenerative changes in the sensory elements. A possible explanation of this distension is suggested by the finding in both cases of certain changes in the saccus endolymphaticus.

A mechanism is further suggested whereby the histological changes may be correlated with the clinical features of the disease.

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REFERENCES

1 Watkyn-Thomas, F. W., and Lowndes Yates, A., "The Principles and Practice of Otology". Lewis and Co., London, 1932, p. 510.
2 Wright, A. J., *J. Laryng. and Otol.*, 1938, **53**, 97.
3 Crowe, S. J., *Medicine*, 1938, **17**, 1.
4 Dandy, W. E., *Am. J. Surg.*, 1933, **20**, 693.
5 Witmaack, K., *Arch. f. Ohrenheilk.*, 1929, **124**, 176.
6 Videbech, H., *Acta oto-laryng.*, 1932, **22**, 51.
7 Eckert-Möbius, A., *Henke and Lubarsch's "Handbuch d. spez. path. Anat. u. Hist."*, 1926, **12**, 89.
8 Guild, S. R., *Am. J. Anat.*, 1927, **39**, 1.
9 Anson, B. J., and Nesselrod, J. P., *Arch. Otolaryng.*, 1936, **24**, 127.
10 Guild, S. R., *Am. J. Anat.*, 1927, **39**, 57.
11 Bast, T. H., *Anat. Rec.*, 1928, **40**, 61.
12 Witmaack, K., *Henke and Lubarsch's "Handbuch d. spez. path. Anat. u. Hist."*, 1926, **12**, 290.
13 Retzius, G., "Das Gehörorgan der Wirbelthiere", 1884, II, 336.
14 Nabeya, quoted by Kolmer, W., *op. cit. infra* 16, p. 365.
15 Belemer, J. J., *Arch. Otolaryng.*, 1936, **23**, 93.
16 Kolmer, W., *Handbuch d. mikroskopisch. Anat. d. mensch.*, 1927 (Möllendorff, W.v. Hrsgbr.), Bd. III, **1**, 348.

Section of Psychiatry

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Spontaneous Drawings as an Approach to Some Problems of Psychopathology

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COLLECTION AND DESCRIPTION OF MATERIAL

MANY authors who have studied the drawings of patients suffering from mental illness, and more particularly from schizophrenic illness, have pointed out that certain superficial qualities (e.g. stereotypy, over-elaboration, or symbolism) are not necessarily pathological, but can often be seen in the playful spontaneous drawings done by normal people on desks, telephone pads, lavatory walls, &c. Such drawings have come to be best known as " doodles ", a word which has been popularized by a recent American film. Everyone knows what they look like, and yet it is not easy to create a definition which does not imply some theory about the mode of production. We have contented ourselves with defining them as " graphic results of playful activity done without purpose, in a state of divided and/or diminished attention ".

Our own interest in such drawings, already expressed in a paper on schizophrenic pictures published in 1937, has recently become more generally shared by the public as a result of a competition run by an evening paper, which not only gave a prize for the examples published, but also provided " an expert psychologist " to inform the world about the personality of the sender, as deduced from his contribution. Such a competition seemed to provide a good opportunity for increasing our own small collection, and a visit to a mildly amused editor resulted in our becoming the somewhat embarrassed owners of all his surplus material, comprising some 9,000 examples of " doodles ", contained in two sacks, each of which it took two men to lift ; each example was accompanied by a letter giving the sender's sex, work, and occupation at the time of " doodling ".

In the past such drawings have usually been looked upon as material for studying the psychology of the individual; they have been regarded like free association or dreams, or *Fehlhandlungen*, as an unveiling of the " unconscious ", drawn involuntarily, regardless of their effect on outside observers, and expressive of

personal qualities. Conclusions may be drawn from them similar to those of the handwriting expert or the physiognomist who makes use of physical features and gestures to analyse character. Such an analysis naturally depends for its verification on a study of the individual artist, a study which was obviously impossible for us to make. On the other hand, our vast and unexpected windfall provided sufficient material to make possible an approach to some problems of psychopathology along the lines of collective psychology.

The variety of people who responded to the competition is shown in the following table :—

Professions :	
(*a*) Higher : Judicial, Doctors, Professors, Clergy, Lawyers	3·5%
(*b*) Lower : Teachers, Nurses, &c.	6·0%
Trades :	
(*a*) Higher : Administration, Managers, &c.	8·0%
(*b*) Lower : Salesmen, Clerks, Typists, Seamstresses ...	25%
Craftsmen :	
(*a*) Skilled : Engineers, Chauffeurs, &c.	12·0%
(*b*) Semi-skilled : Factory hands, &c.	5·0%
Services	2·0%
Unskilled labourers	2·5%
Domestic workers	7·0%
Creative :	
Artists, Musicians, Actors, Authors, and Architects ...	13·0%
Students	7·0%
Housewives	6·0%
Leisured classes	4·0%

This list is shown merely to give some idea of the social class, as it is impossible to form an opinion of any value as to why these responded. They may represent ordinary readers of the evening paper, or be those who would enjoy any form of newspaper competition ; they may be people who always have a paper and pencil somewhere within reach, and who are, therefore, more apt to indulge in this pastime, or they may have to do a lot of hanging about and waiting in the course of their work, as suggested by the large number of typists, clerks, &c. The considerable percentage of competitors who do some creative work is of interest, though it might have been anticipated. In any case, for the purpose of study, they form a fairly varied and representative group of middle-class town dwellers.

The proportion of males to females was 3 : 2, which is surprising, as women are supposed to be more inclined to enter for newspaper competitions. Our finding is perhaps explained by their being less likely to read evening, as opposed to morning, papers, or possibly because they are less creative.

Many examples were sent in by children or by their parents, but these have been collected into a separate group for comparative study.

The material has certain obvious advantages and disadvantages. It can be looked upon as the outcome of a very unusual and striking mass experiment ; thousands of average people provided mental products which are largely independent of educational or traditional influences of any kind. No conventions, no fashions, are in existence to tell people what such a drawing should contain or what it should look like. There is no recognized standard of "doodling". Few people know how famous

men have scribbled and nobody tries to imitate the appearance or style of anyone else, e.g. his teacher or personal hero. To appreciate the peculiar spontaneity, one has to bear in mind how difficult it would be to think of any similar independent competition which could be used for an average population. If, for example, people were asked to write a story for children, to compose a limerick, to describe dreams, or to send a love-letter which they thought the most beautiful, &c., the tradition in language, the literary tastes and fashion, would restrict the choice. Moreover, uniformity in speaking and thinking, as determined by newspapers, cinema, and wireless, would become obvious and would obliterate individual differences as soon as the number of competitors grew large. This may be illustrated by the result of a competition to suggest a new name for a cigarette which took place in Germany some years ago. There were over 100,000 competitors, of whom more than one-third proposed the same name. More recently B.B.C. listeners were asked by a dance-band conductor to suggest a title for a dance tune. Out of 600 suggested titles more than 70% included the words " I dream ". The restriction of competitors would be still greater if a drawing for a special purpose or on a special topic was requested, for language and writing are at everybody's disposal, whereas artistic ability is rare. It is very striking how far in this experiment such psychological inhibitions and all the forces which usually act in collective psychology are excluded. Religious, philosophical, or political conventions of thinking, behaviour patterns of professions, race, social level, " psychological infection ", mass suggestion, imitative instincts, and the lower instincts which make human reactions so monotonous, all these can be regarded as ineffective, or as relatively ineffective. There was, in fact, the fullest liberty imaginable in the sphere of mind. Paper and pencil as tools to be used were the only common, restricting factor, the influence of which will be mentioned later.

Certain obvious objections to the material stand out: Examples were sent in for competitive reasons as well as for interest; consequently it is reasonable to infer that only those of some impressiveness were likely to be sent in. Actually, large numbers were so poor in execution and so dull in content that it was a matter of surprise that anyone had troubled to send them, and it could only be presumed that the criterion considered most important by the sender had been that the example should be genuine. None the less it is probable that the standard of originality and artistic accomplishment is above that of the average population. In this respect the number of senders belonging to some artistically creative profession is of interest.

The possibility of publication, and perhaps the social class of the senders, would also preclude the sending in of pornographic drawings. It is our impression that they are relatively rare in any case, but that they exist is certainly true.

The question of how far the published material may have influenced the originality and genuineness of the examples presented is difficult to judge. A few may have been copied or elaborated, but it was remarkable how frequently senders mentioned that they had collected their contributions from the past, from old scrap-books, &c., while others sent examples which they had found by chance on the desks of their superiors or elsewhere.

Bearing on the same question is the fact that only a single individual example was available, so that it was difficult to know whether it was representative of the sender's usual habits. Frequently, however, it was specifically mentioned that they always drew the same thing, or had a restricted number of methods, e.g. " I always draw faces ". " I always make geometrical designs." " I invariably fill in letters or make circles." Personal inquiry suggests that most people have one or two favourite styles which, however much they may vary in detail, would usually be recognizable as their own.

Classification of Material

In going over the material together, certain points of interest crystallized out which formed the basis of classification. It was then possible for each of us to work separately in order to examine a large mass of material, and to show by comparison of results that the personal factor did not importantly determine the statistical findings.

The material was dealt with without choice as it came out of the sack, and it soon became apparent that two methods of classification were necessary: (1) According to the composition of the whole, and (2) according to the content.

Composition (*see* Plate I).—Each example could be allocated to one of the following five groups: (*a*) Scenes (fig. 1). These resemble an ordinary picture in that they are realistic representations of one recognizable subject. (*b*) Medley (fig. 2). Stray items independent of each other, separated by an empty space, generally of about the same size. Although there may be some psychological connecting link in the content, they are separated like a collection of photographs on the page of an album. (*c*) Mixture (fig. 3). This, too, contains items, each with their own content, but they are not separated as in a medley, but run into each other and intermingle, so that one line may belong to two groups and have a different meaning in each. (*d*) Scribble (fig. 4). The least elaborate products, consisting of lines and scrawls. (*e*) Ornament (fig. 5). Consists only of a stylized decorative pattern.

Percentages.—Scenes, 11; medley, 38; mixture, 32; scribble, 7; ornamental, 12.

The *content* of the drawings was analysed and classified in the following way: Each might show one or all of the following features, which were represented in the following percentages: Stereotypy, 30; ornamental detail, 60; figures, 38; animals, 35; objects, 55; faces, 60; movement, 16; numbers, 37; writing, 60.

The small percentage which could be classified as scribbles is presumably due to artificial selection; they were not considered worth sending, but they are an important group as they represent the lowest level in the grades of spontaneous drawings of this kind, just as they represent the earliest artistic efforts of children and probably of primitive man. E. T. Cooke has said "neither the child nor primitive man begins with a geometrical line, the history of graphic art is hidden in a scribble".

The development of drawing from the scribble is a controversial subject. In children the lines become more rhythmical and stereotyped, and then there follows representational art and the introduction of ornament. In primitive man it is quite uncertain whether ornament or representation was the original form of art. Both were present in palæolithic times and, as Charlotte Bühler has pointed out, it is possible to imagine that there could be a transition from scribbling to ornament as well as to representation. In our classification the small number of purely ornamental drawings (12%) is balanced by the large number in which there is much ornamental detail (60%). Representation of faces, figures, animals, and objects, occurs in a large number. Faces especially are frequent, occurring in 60% of all the examples. This is again understandable in the light of children's drawings, for it has been observed that up to the age of 10 children draw the human face and figure in preference to anything else, animals being the next favourite subject. In our material there was a marked tendency to mix representational with ornamental (Plate I, fig. 6), to turn a geometrical design into a face or symbolical object (Plate II, fig. 7), or to add ornamental detail and elaboration to purely representational drawings (fig. 8). A similar tendency can be seen in the drawings of many schizophrenic patients (figs. 9 and 10). There is no borderline between form and content, a point which will be discussed later, but it is of interest to note that one sender makes the observation: "The enclosed was done during a telephone call, the elaborate bits while holding on, and the padding while talking."

PLATE I.

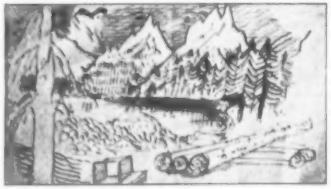

FIG. 1.

FIG. 2

FIG. 4.

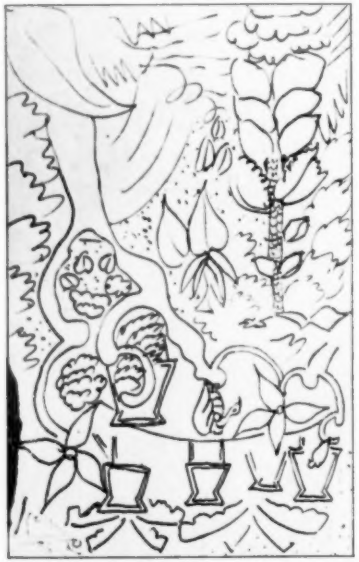

FIG. 3.

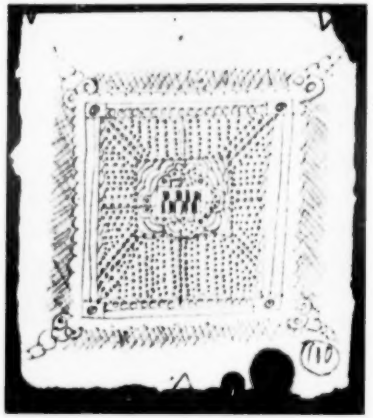

FIG. 5.

FIG. 6.

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PLATE II.

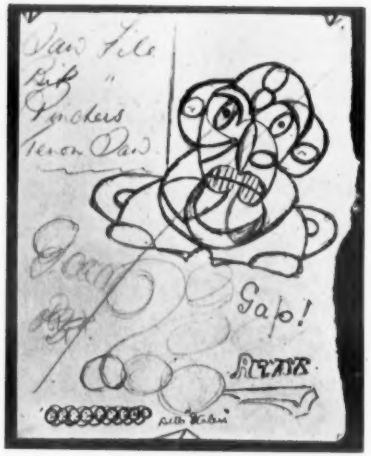

FIG. 7.

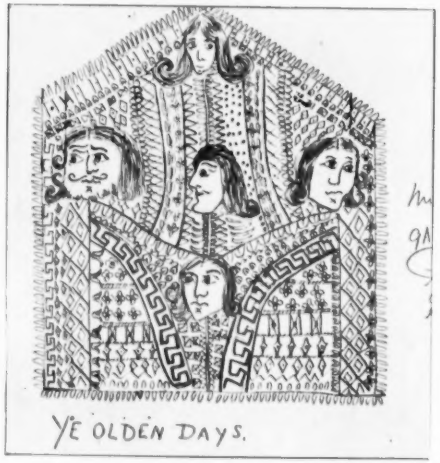

FIG. 8.

FIG. 9.—From "The Diary of Nijinsky".
(Reproduced by permission of the publishers, Messrs. Gollancz, Ltd.)

FIG. 10.—Drawing by a chronic schizophrenic patient.

PLATE III.

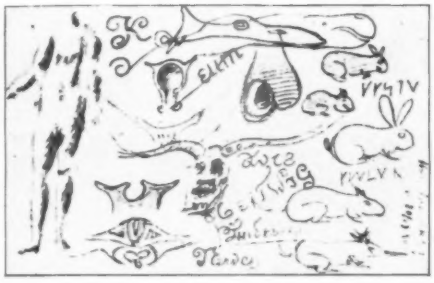

FIG. 11.—By a gynæcologist (from M. Grotjahn, *Med. Welt.*, 1932, reproduced by permission).

FIG. 12

FIG. 13.

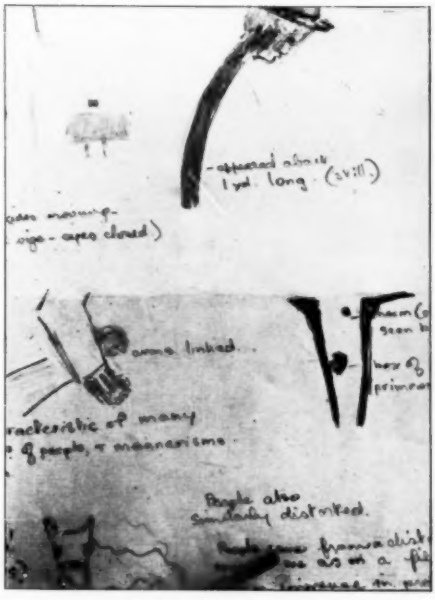

FIG. 14.—Fleeting hallucinations seen and drawn by a schizophrenic patient.

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FIG. 15

FIG. 16.—Original stimulus was a single blot which now forms the native's mouth.

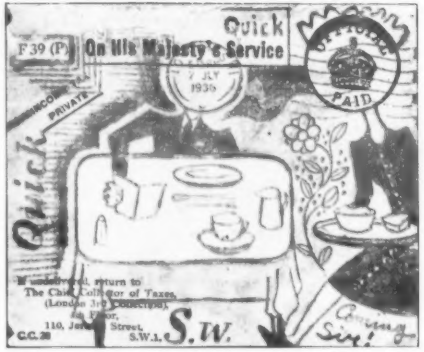

FIG. 17.

FIG. 18.

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The tendency to have a variety of disconnected items, as shown in the large percentage of examples which fall into the mixture and medley groups, totalling 70%, is also parallel in the drawings of children. Small children tend to make disconnected and fragmentary pictures, and Stern has pointed out that it is characteristic of the child's imagination to jump from one thing to another; he further suggests that in this is found the dividing line between the imagination of the child and that of the artist. Some patients with mental illness, among them some artists, have shown a regression to the child's level and produced pictures consisting only of a muddled and disordered mass of detail.

Among the more elaborate specimens the content may reflect the profession of its creator (Plate III, fig. 11), his preoccupation (fig. 12), or his occupation at the time of creating (fig. 13); thus in 12% the content was clearly influenced by the sender's usual work, in 25% by his actual occupation at the time of drawing, and in many there could be seen preoccupation with current events, as typified by cartoons of Hitler, Mussolini, cinema stars, or swastikas, sickles, guns, &c.

The *size* of the specimen sent varied between a bit torn from the margin of a newspaper to a full-size blotting sheet from a writing desk. An architect submitted the paper covering of his desk, on which were collected the results of many years of industrious scribbling.

The size, as well as the material used, apparently depends on chance to a large extent. Newspapers, blotting paper, bridge blocks, have been used because they were just at hand. The influence of the material—lines, print, creases—will be dealt with later.

More interesting is the size of the single objects portrayed in the drawings. Their smallness is striking, a fact which it was easy to investigate in the human faces and figures which were so common. 200 specimens were analysed for this purpose. 141 of them contained faces and/or human figures. Only 10 faces were more than 1½ in. in diameter, only one of them more than 5 in. There may be several explanations for this self-imposed limitation. For instance, the size of the drawings corresponds roughly to the size of the photographs that every citizen sees every day in his newspaper. But it is quite possible that their size and that of the magazine picture has some physiological foundation. In this respect it is interesting to remember the micropsia which can occur in certain toxic states, or the small fleeting hallucinations that may occur in acute schizophrenia, and which can sometimes be illustrated by the patient (Plate III, fig. 14).

Another factor determining the size of the picture is the technique in which it is done. The painter who paints a portrait on an easel is likely to use his elbow- and shoulder-joints in making movements; they will therefore tend to be bigger than those of a man who draws or scribbles on a writing desk, using mainly movements of his wrist and his fingers.

The placid or lazy state of mind while making "doodles" also favours, if anything, actions with restricted movements. We know from pathology an example of the opposite. States of excitement may be foreshadowed by the artist choosing bigger sizes for his canvasses, e.g. Van Gogh. The individual stroke of the brush may also become bigger as the excitement begins.

Turning now to the presence of *writing*, one can say that these drawings are not primarily intended to be an expression, a carrier of meaning, and yet writing is frequently present as if in the course of the process this tendency came into it and influenced it. The individual finds himself in the middle of an undertaking with which he really cannot cope; he wants to put on paper something that cannot really be put into drawing. What can he do except resort to his ordinary method of

expressing something on paper ? He switches over to writing. Out of 500 specimens, numbers were found in 187, writings in 293 ; usually both were present. Only 139 showed neither. It is debatable whether some stereotyped patterns, such as the cat or the rabbit, may not serve the same function. Cats and rabbits were present in 45, swastika, union jack, &c. in 38, making a total of 20%. On the other hand, it could be argued that letters and numbers are the most automatized symbols and must necessarily come to the surface in such states of consciousness as we assume to be present. It is, however, interesting to note that these drawings are hardly ever begun by writing (as far as one can judge), and that with few exceptions the symbols generally play only a very secondary role.

This view of the significance of the presence of writing is corroborated by what we found previously in drawings of the insane, and can be regarded as a sort of mutual confirmation. One can observe in patients how, with the increase of the morbid activity and psychopathological productivity, their means of expression in drawing or painting fall short of their intentions, and thus they start writing into their pictures.

Psychological Situation

Attention.—The psychological situation in which this activity can take place must now be considered. It can be said that " doodles " are produced in idleness, boredom, leisure, meditation, or in states showing affective tension, such as indecision, concentration, expectation, and impatience. In these states three types of alteration of attention may be distinguished, (*a*) diminution, (*b*) division, and (*c*) fluctuation, though they may occur in combination.

(*a*) If one speaks of an idling or bored person's attention as diminished, it means that he does not respond easily to outer stimuli, his mental processes are slow, emotions weak, and his ideas lack energy. There is little influence of outside stimuli and of determining ideas on the thought. (*b*) For an analysis of divided attention one has to review the various activities with which spontaneous drawing may share attention : Occupied with a problem, planning various things, listening to lectures, conversation, or music, waiting for something special. In such states the person is capable of responding to outward stimuli with his usual promptness. All other mental processes are also unimpaired within the prevailing field and determination of the thought-process is intact. At the same time a second field exists in which attention is lowered, as already described. This is the domain of doodling. Under certain circumstances attention may be concentrated for a short period on the second field, but very soon is shifted back to the main topic. (*c*) Such fluctuations may occur without pre-existing division of attention, i.e. the attention wanders from time to time from the principal occupation into the side-line of drawing.

State of Consciousness

Attention is often used as a criterion, and sometimes wrongly regarded as the only one, of the lucidity of consciousness. There can be little doubt that in states of diminished attention, e.g. when idle, the lucidity of consciousness may be decreased to a somnolent state. This brings " doodling " into the neighbourhood of hypnogogic states in which there is a predisposition for visual hallucinations of a specific kind. It may be another manifestation of the same predisposition. In pathological conditions a similar state of consciousness may be observed with increased intracranial pressure or with slight intoxication, e.g. by bromides, &c.

Divided attention need not necessarily be accompanied by a dimming of consciousness. The very alert and active man is able to distribute his attention between

the main line of his actual occupation and its side lines. A typical example of this behaviour is the perfect hostess, who apparently gives her full attention to each guest who converses with her, and still observes all her other duties with clock-like precision. She never loses herself, each of the many sequences of ideas which are simultaneously present in her mind is ready to take the lead at the appropriate moment.

The state of the " doodler " differs from that of the perfect hostess in that the distribution of attention in the former is quite unequal. His secondary occupation, i.e. drawing, is pushed far to the periphery of his consciousness, but the general lucidity is unimpaired. As a counterpart in pathology the so-called double orientation of schizophrenics can be quoted.

Fluctuations of attention in " doodling " always indicate fluctuations of consciousness. The subject turns from a state of full concentration into the attitude of relaxation. The situation can be compared with that of a tired traveller who falls asleep over his book but wakes up whenever the speed of the train changes. Similar fluctuations occur pathologically in delirious states. If the disturbance of consciousness is not very deep, the patient can be roused and brought into touch with reality, but very soon he slips back into his dream world. It is noteworthy that delirium again predisposes for visual hallucination.

Mental Attitude

Turning to the list of psychological situations given above, one must enlarge to a certain extent on the short remarks contained in the accompanying letters. Idleness and leisure are not so often present as might have been expected. They are sometimes named as such, but more often described in terms of " on train ", " smoking ", " resting ", " tired of books and knitting ", and most commonly as " listening to the wireless ".

Boredom.—Already containing some muscular unrest, it certainly plays an important part as an underlying condition ; it is seldom plainly expressed, but can be suspected in remarks such as " doodled in conference ", " during sermon ", and, in many instances, during lessons or lectures.

One cannot, of course, be certain that on these occasions meditation, or even concentration, may not have conditioned the production, and that these states also favour it is proved by letters stating that the senders made their drawings while " deep in thought ", " solving business problems ", or " dictating letters ". Schoolboys and students do them during homework, teachers when preparing lessons. Many competitors describe their occupations as " thinking ", which may, of course, mean anything.

Indecision.—This is more or less plainly expressed in statements like : " making up my mind ", " making holiday plans ", " seeking inspiration " (an artist), " working on essay " (an art student), and in these numerous cases in which " letter writing " was accompanied by spontaneous drawing. There is nothing to be gained by giving figures of these single psychological situations as their description is not sufficiently precise.

Emotional attitude.—The large number of examples drawn in a state of *expectation* is shown by the emotional attitude which accompanies the drawings. Two main groups contribute to it, " waiting ", and " telephoning ". Waiting is sometimes more explicitly defined as " at hairdresser ", " at the dentist ", " for a letter ", or—quite frequently—" waiting for football scores or racing results ". There can be little

doubt that *impatience* is the common affective factor, however the situations and personalities may differ. Impatience is alleviated by graphic activity of this kind, so are boredom, futile concentration, and indecision.

Four main groups were formed in order to show the mental attitude among 433 persons who gave conclusive records about their occupations while actually at work on their drawings.

	Number	Percentage
Complete idleness	28	6
Passivity, e.g. listening to radio	93	20
Working at a problem ...	111	26
Expectation (e.g. telephone) ...	188	45
Miscellaneous	13	3

From these figures there is clear evidence of how greatly splitting of attention and a certain amount of motor tension favour this activity. Thus an obvious subdivision of our material results : One-third is done in a resting, passive attitude, relaxed and relatively free from actual emotional tension, often while listening to music. Two-thirds, however, originate in a tense and restless state, and can be regarded as an outlet of the actual affective behaviour.

Tension and relaxation.—In order to find the correlation, if any, between the state of mind of the producer and the form and content of the product, those cases were marked in which the accompanying notes allowed a classification into (1) state of tension (T.) or (2) state of relaxation (R.). T. was mainly represented by waiting—in a considerable proportion, waiting at the telephone, often with additional remarks pointing to the impatience of the person. The R.'s were generally listening to the wireless.

50 T.'s and 50 R.'s were collected at random, and the corresponding data in the columns headed scenes, medley, mixture, scribbles, ornament, were counted. The results are given in the following table :—

	Scenes	Medley	Mixture	Scribble	Ornament
Tension	6	18	22	2	5
Relaxation	5	18	14	2	11

The significant result appeared to be that the state of tension favours the at-random collection of items as characterized by the mixture, while a state of relaxation favours the elaboration of total ornaments. The suggestion that drawing in this way may be an outlet for motor tension introduces the idea of an objective purpose for this subjectively purposeless activity. The question of the relationship of the psychological situation to the purpose of the drawings leads to other interesting distinctions.

Spontaneous Drawing as a Recreation

In a series of cases, the drawing seems a pure pastime, an idle play, without aim or end. It appears to be the only manifest activity of the person who is idling, or "thinking". Some competitors, however, stated that they did it "to distract their thoughts" from unpleasant contents. Its aimlessness becomes even more doubtful when one sees that in other cases the drawings are a kind of by-product of serious professional work. Architects, designers, and artists, sketch absentmindedly in intervals between drawing or designing. They not only try out their pencil or whatever other tool they use, but also practise their imagination and at the same time relax from concentrated working. This relaxation is known to be indispensable in creative production and has often been described by artists. As might be expected, several

of the most original examples in our material belong to this category, i.e. come from artists' desks (Plate IV, fig. 15).

It can be presumed that many of the letter-writers and some of the other contributors behaved in similar ways, e.g. waiting for an idea for solving a crossword puzzle (a frequently described situation), seeking inspiration, preparing lessons, and so on ; they all reveal a recreative function which spontaneous drawing shares with other kinds of play. It serves not only as recreation from concentrated work, but also from mechanical repetitive activities like " memorizing ", " transposing music ", &c.

Sensory Stimulation

One large group, however, shows no apparent purpose. I refer to those who " doodle " while listening to something, usually music, but also to lectures or conversation. *Auditory perception* here may act as the stimulus of a playful activity, a relationship for which it is hard to find a rational explanation. Even if musical notes or names of composers are found among the scribbles, what it is that provokes the activity proper remains in the dark. Rhythm, of course, is common to both the auditory and motor fields, and the drawings, inasmuch as they contain repetition and ornaments, can be regarded as rhythmic documents. Erwin Straus has described how auditory space is more primitive and structureless than visual, and how directions like front and back, horizontal and perpendicular, do not play any role. The lack of spatial order and economy in many of the drawings may originate from their stimulation by hearing, but it is just as possible, or more so, that it is due to the same factors as cause it in children's drawings.

Visual stimuli.—The influence of visual stimuli on spontaneous drawing seems easy to understand (Plate IV, figs. 16 and 17). Dots and lines on blotting paper serve as a stimulus for scribbling, and, at the same time, by their forms, direct the content, an effect which occurs in all such drawings after the first line or curve has been made. Everything that follows may be grouped around it if the person is susceptible to the visual impression of his own drawing. The process of drawing is here, as in any other artistic production, directed by the to-and-fro effect between artistic aim and visual reflection of the work in progress. " The visible work on its way to completion influences psychologically the process of its completion." As there is no consciously recognized aim in spontaneous drawing, the visual stimulation can be expected to be correspondingly more effective.

This influence of definite visual stimuli on the special form of the product is indisputable, but vague perceptions of indistinct shapes and patterns can also start a person drawing, just as they can normal visual fantasy, e.g. seeing things in the fire, or in the clouds, or in foliage (Plate IV, fig. 18). Seeing illusory figures or faces in the dark is a common happening in childhood and a characteristic symptom in psychotic states like delirium, i.e. in states of clouded consciousness. As a lowering of the level of consciousness is one of the predisposing conditions for " doodling ", its relation to the visual fantasy production seems worth considering. Rorschach's ink-blot test makes use of this human faculty as a method of diagnosing personalities and psychological anomalies, and because it is, like spontaneous drawing, relatively independent of intelligence, education, and cultural background, it has proved more easily applicable and more reliable than most other personality tests.

The difference between such optical illusions and the active formation of drawings should not be overlooked. It can scarcely be assumed that spontaneous drawings are nothing but a tracing of lines which the visual imagination creates on the background of shapes present on the paper.

Motor Behaviour

Apart from the question of visual stimulation, if spontaneous drawing is to occur, there must be a motor drive which leads to the process of drawing and plays a decisive part in it.

Spontaneous drawing only occurs in the absence of other movement, but this motor inactivity differs greatly in its psychological character in different cases. In only a small number is there total relaxation. In a considerably larger number the motor activity may have been released by some auditory stimulus, as has been discussed, but in by far the largest proportion there is a kind of motor tension due to being forced by environmental circumstances, such as waiting in a telephone box, to restrain the motor drive which might normally express itself in pacing up and down the room or talking. A doctor expressed this clearly when he said, " I never doodle. O yes, I do, I do it when I am impatiently waiting for a patient to stop talking so that I can say something ". Individuals differ in the way they get rid of muscular tension accompanying emotions. Trembling, fidgeting, scratching, playing with different objects, can be observed, and " doodling " may be a substitute for any of them. The idea of overflow of motor energy is familiar in many psychotic states, dominated as they may be by hyperactivity which has no apparent psychological motivation. In schizophrenia this hyperactivity often lacks even an emotional colouring, and the surplus of energy produces restlessness or states of motor tension. The activity is aimless and poor in content. It has, therefore, a repetitive character and shows perseveration, a characteristic which we meet again and again in spontaneous drawing. This quality has been noted by all writers who have been interested in either subject.

Repetition and Stereotypy

In the analysis of the content of the drawings stereotypy was noted in 152 cases (out of 500) (Plate V, figs. 19 and 20). But a large number of the 292 specimens that contained ornamental detail showed features that could also be classified under the heading of stereotypy.

There is a tendency to perseverate in many fields of nervous function, in imagery, associations, thought, or motor action. Perseveration has been studied most intensively in the field of associations. Every idea that has been in consciousness once has a tendency to re-enter consciousness, and this tendency increases the more intensive the idea has been, the more frequently it has existed before, or the less consciousness is filled by something else. This last applies to spontaneous drawing, but apart from that, it must be remembered that repetitive movements lead to lowering of the level of consciousness ; rocking movements of the cradle, patting, the methods to induce hypnosis, all have the same effect. In many states of dissolution of the function of the central nervous system, such as senility, encephalitis lethargica, or idiocy, repetition occurs as a symptom. The activities often have a rhythmic quality as well. The same can be observed in children, among whom repetition of the same movement, the same sound, the same question, is very common. With backward or feeble-minded children, however, this tendency to automatism is much more frequently observed than in the case of normal children, and it seems to have a more purely automatic character (Goodenough). The acquisition of purposeful movement seems to be a function of the cerebral cortex which consists in re-distributing the rhythmical motor discharges, discontinuing the rhythm. On the other hand, if the cortex stops functioning, rhythmic, repetitive, stereotyped activity comes to the surface again.

" *Mescalin type* " *of drawings.*—Stereotypy, or something very similar, may also occur in an entirely different way. There are a number of examples which we felt

PLATE V.

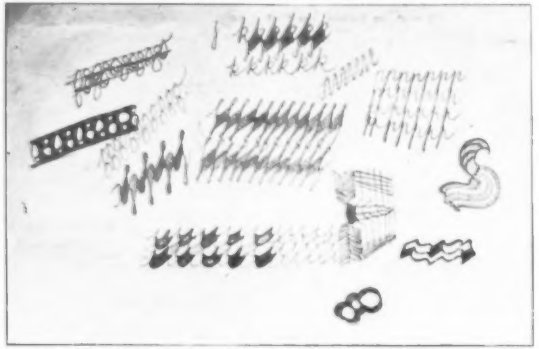

FIG. 19.

FIG. 20.

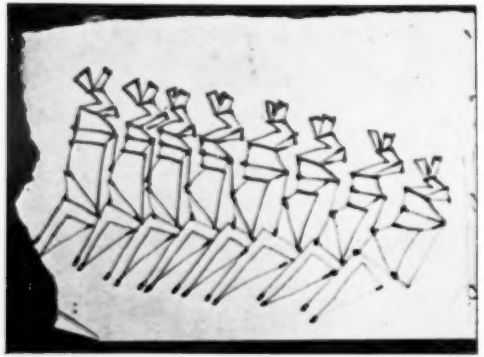

FIG. 21.

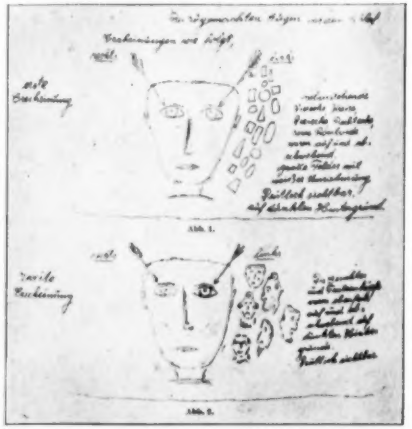

FIG. 22.

(From Engerth, Hoff and Pötzl, *Ztschr. f. d. ges. Neurol. u. Psychiat.* 1935. Reproduced by permission.)

PLATE VI.

FIG. 23.

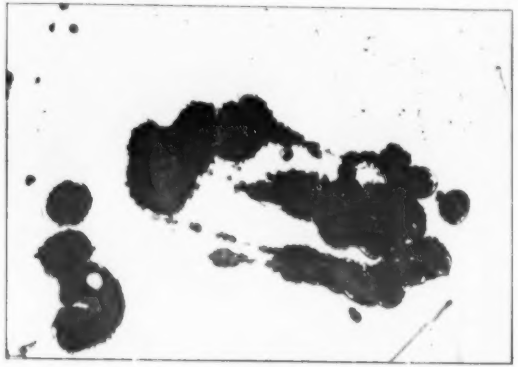

FIG. 24.

FIG. 25.

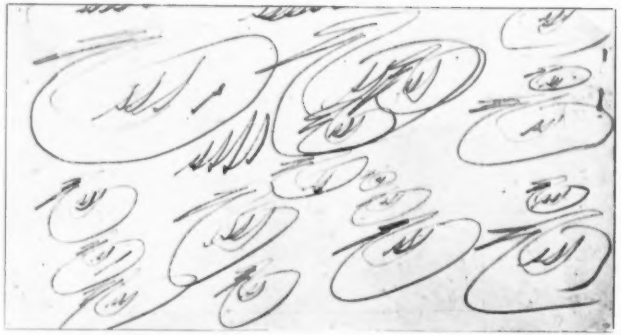

FIG. 26.

impelled to call the " mescalin type " (Plate V, fig. 21). They are characterized by the repetition of similar, parallel, linear elements, often varying in size, either gradually increasing or decreasing, sometimes giving the impression of perspective, in short, exactly what people under the effect of mescalin describe and sometimes illustrate. Similar occurrences are known after focal brain lesions, probably localized in the occipital cortex. Polyopsia has been defined by Pötzl as " seeing an object multiplied, the multiple images arranged in rows, or like a string of beads ". He published several cases of this kind, in which occipital lesions could be verified either by operation or by post-mortem examination. One of them (Plate V, fig. 22), an artist, is of special interest because he could draw his visions, and demonstrated in this way how the primitive patterns gradually developed into shapes of higher integration (faces, Christmas-tree lights), a process which can also be observed in mescal intoxication, and which also may be of importance in the development of what we call the motor-sensory type of spontaneous drawing.

Genetic Classification

Turning again to the psychological situation, we attempted to judge from the appearance of the drawings what were the influences at work in their genesis. We established three categories, namely, sensory, motor, and realistic.

Sensory (Plate VI, figs. 23 and 24).—Drawings in which visual stimulation was either operative from the start or played a leading part in further execution. Leonardo da Vinci said :—

" This method of looking at fortuitous shapes may stir the mind to invention and can therefore be of importance for creative work. If you stare at stained and spotted walls or at embers in the fire, or clouds, or mud, you will make marvellous discoveries in them, compositions of battle, of men and animals, rocks, trees, mountains . . . grimaces, costumes and innumerable things which you may mould into perfect shapes, for the spirit is awakened to new invention by diffuse and indefinite things."

Motor (Plate VI, figs. 25 and 26).—Drawings in which the motor element prevailed in their production and in which, from the order of the strokes, no clear visual influence was discovered. Gottfried Keller has described such a drawing by himself :—

" I had been drawing not more than half an hour when I dropped into a state of profound distraction and went on pencilling without thinking, as if I would try out a pen. I went on scribbling and gradually added an infinite network of pencil strokes which I enlarged every day in brooding, as often as I intended to start work. Finally, the monster which looked like a huge grey spider's web covered the larger part of the paper."

Realistic (Plate I, fig. 1).—Drawings belonging to neither of the above groups and representing some part of reality as a " picture". Pfeiffer describes this type when he writes about drawings by adults, and says : " The first step in drawing is a reproduction of visual images which approximately correspond to the object to be drawn in size, shape, and contour. One can often hear a person saying when getting ready to draw something, ' I am looking for a sheet of paper . . . no, that is not the right one, it must be bigger '." The picture is imagined already on the paper, though possibly not very clearly and definitely, but this picture, once sketched, dominates the whole further procedure.

There were, of course, a considerable number which could not be put into any of these three categories ; some were motor-sensory, others sensory-motor, while others probably fluctuated during the drawing process. The criteria were not very precisely defined, so that a certain amount of individual differences in classification could be anticipated. Nevertheless the results are of some interest and, out of the 409 which

Fig. 25. W. S. MAYER-GROSS and W. MAYER-GROSS : Spontaneous Drawings as an Approach to Some Problems of Psychopathology.

Fig. 26.

could be classified, approximately one-third belonged to each category, 30% sensory, 35% motor, 27% realistic.

More interesting is the correlation between the mental state of the doodler and the " genetic " type of the doodle, i.e. the motor, sensory, or realistic group.

The results in this respect were :—

	Total	Motor	Sensory	Realistic
Tension	50	26	9	9
Relaxation	50	14	13	8

That is to say, the state of tension leads to a mere motor discharge in a large proportion of the cases, while relaxation favours the digestion of the motor product and its elaboration in the light of the visions seen into it.

Collective and Individual Psychology

In conclusion, we would like to point out the paradoxical nature of this investigation. Its material is the outcome of a large mass-experiment, promising insight into the problem of collective psychology, and yet it has been found that each individual example taken from this material was made in an atmosphere of complete isolation of the individual, for which imprisonment in a telephone box can be taken as the standard symbol. This independence from all the usual influences of mass psychology has been described in the introductory chapter. The drawings are either thrown away or hidden when there is no competition to entice them into the full daylight of publicity. Doodling can be called a most asocial activity ; there is no community of people who make doodles—not even a suggestion in any of the letters of any two people combining in a joint effort.

The method of choice for gaining some insight into the psychology of spontaneous drawing was, therefore, of necessity, that of the psychology of the individual. The results yielded have justified its application. Single observations were confirmed in a great number of examples, and statistical interrelations could be established. Grouping of the material proved unexpectedly easy, and the viewpoints taken from one were found applicable to many. The isolation, freedom, and independence from standard influences, had not the effect one might have expected. The products of free phantasy were conformable with a few types, and to a large extent could be called monotonous. Thus the collective character of the material became obtrusive again in spite of the individual approach chosen. To explain this uniformity it must be remembered that the relative uniformity of psychological reactions in man has been demonstrated in other situations by other observers.

Uniformity of human reaction.—If, for example, a large number of subjects are asked to write down a figure between 1 and 10, 11 and 20, 21 and 30, &c., in the majority of cases figures with the final digit 5 are chosen, and every other figure is as much rarer as its last digit differs from 5. If people are asked to write down the name of a colour, the majority will write " red " ; " blue " and " green " follow. Even if a great many persons are asked to write down some word that just comes into their mind, the reactions are identical to a large extent. (In an experiment of Marbe's, 199 out of 350 subjects noted a word that occurred at least in one other case.)

Similar preferences for numbers can be found if one investigates, for example, the number of years of imprisonment to which people have been convicted. In 1888, according to Havelock Ellis, 6,970 persons were in English gaols. Among these, 3,034 had sentences of five years, while only one person had a sentence of six and a

half years, 1,022 persons were sentenced for ten years, but only one for eleven, six for nine years, 240 persons had a sentence of twenty years, but only three had twenty-one years. Galton records that in the original table in the Blue Book there were no sentences of seventeen months, but 32 of sixteen months and 340 of eighteen months.

Similarity of reaction depends partly—as has been shown in association experiments—on upbringing, education, and the social class of the subjects. But other investigations have demonstrated such similarities in most widely varying periods and cultures. The final digits in the numbers of ages on Roman tombstones, the decimals that persons guess when asked to estimate lengths, the last digits of the ages given in the census of an illiterate population in Alabama, show the same order of frequency (0, 5, 8, 2). "This uniformity", says Marbe, "is apparently not a product of civilization but is founded in the psychological properties of man". Such observations bring our results into line with known facts, but do not offer an explanation.

As a second consideration it may be mentioned that a relative uniformity must result if one deals with a very great number of objects. This, of course, is only true if the proportion between classes and number of objects to be classified is used as a measure of uniformity or otherwise. It becomes the more conspicuous the more the subdivision of the classes is limited. The subdivision of categories contains indeed the cardinal issue of our problem.

In our attempt to subdivide the products of spontaneous drawing, we soon realized that there was a lack of descriptive terms or adequate comparisons for characterizing the material. In spite of our reluctance, we were easily led to use terms from pathology, and to interpret by analogies, the restricted value of which seems obvious. That there is such a poverty of categories seems, however, essentially due to a factor connected with the process of "doodling". We have tried to characterize it as a lowering of the conscious level. It holds generally true that products on a lower niveau of mental activity are difficult to analyse in terms of logic. The same problem is encountered in children's drawings, the behaviour of the insane, and in phenomena of a lower level of evolution. Myths, sagas, fairy tales, superstitions, and other cultural customs of primitive races, offer the same difficulty for a rational classification. Therefore, they appear uniform to a degree which has impressed ethnological observers. The lowering of consciousness brings doodles into the same line. It seems appropriate to speak of this common character as "primitive". It is interesting to see that in spite of the segregation and isolation of the doodler, trends of collective psychology become active.

Similar ideas are contained in Jung's conception of the collective unconscious. He also met with a surprising uniformity of psychological contents in, what he called, deep analysis. It is noteworthy that Jung's school also makes use of drawings, including spontaneous drawings of our kind, for psychological interpretation in analysis.

The analogy between morbid mental symptoms and primitive behaviour has been enlarged upon by many authors. There is no doubt that, in spite of evident analogies, the way by which the lower level is arrived at by patients differs considerably from the behaviour of primitive races. The similarity of the level reached makes an exchange of interpretations possible from one field to the other, and it seemed permissible to try to use the phenomena of spontaneous drawing as a method to throw further light on this problem.

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REFERENCES

ARUNDEL, R. M., "Everybody Pixillated", Boston, 1937.
ELLIS, HAVELOCK, *See* Marbe. *Op. cit. infra.*
ENGERTH, G., HOFF., and PÖTZL, O. (1935), *Ztschr. f. d. ges. Neurol. u. Psychiat.*, **152**, 399, 433.
GALTON, F. (1895), *Nature*, **52**, 174.
GOODENOUGH, F. L., "The Measurement of Intelligence by Drawings", New York, 1925.
GROTJAHN, M. (1932), *Med. Welt*, **6**, 1045, 1082.
GUTTMANN, E., and MACLAY, W. S. (1937), *Brit. J. M. Psych.*, **16**, 184.
MARBE, K., "Die Gleichförmigkeit in der Welt", 2 vols., München, 1916 and 1919.
NIJINSKY, R. (1937), "The Diary of Nijinsky", London.
PFEIFFER, R. A., "Der Geisteskranke u. sein Werk", Leipzig, 1923.
PRINZHORN, H., "Die Bildnerei der Geisteskranken", Berlin, 1922.
STRAUS, E. (1930), Nervenarzt, **3**, 633.